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(71) Applicant(s)
AstraZeneca AB
(Incorporated in Sweden)
151 85 Södertälje, Sweden

(72) Inventor(s)
Ash Bahl
Matthew Perry
Brian Springthorpe

(74) Agent and/or Address for Service
Francis John Tierney
Astrazeneca, Global Intellectual Property, Mereside,
MACCLESFIELD, Cheshire, SK10 4TG,
United Kingdom

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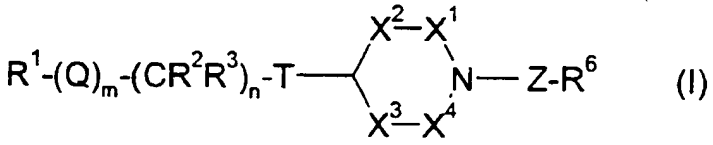
(54) Abstract Title
Pharmaceutical combinations of a CCR3 antagonist and a compound which is useful treatment of asthma, allergic disease or inflammation

(57) The invention provides a pharmaceutical combination comprising a compound of formula (I):



(I)

wherein R^1, R^2, R^3, R^6, Z, Q, m, n, X^1, X^2, X^3, X^4 and T are as defined in the specification, and a histamine antagonist, a steroid, a leukotriene modulator, a human cytokine, a beta-agonist, a phosphodiesterase inhibitor or an antibody; a process for preparing such a combination and the use of such a combination in therapy (especially the treatment of asthma or rhinitis). In particular, the compounds of formula (I) are substituted piperidines and substituted 8-azabicyclo[3.2.1.]octanes and are described as being CCR3 antagonists.

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(58) Field of Search
UK CL (Edition T) **A5B**
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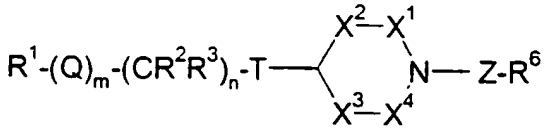
PHARMACEUTICAL COMBINATION

The present invention relates to a pharmaceutical combination comprising a piperidine CCR3 antagonist compound and compound useful in the treatment of asthma, alergic disease or inflammation, to a process for preparing such a combination and to the use of such a combination in therapy.

Chemokines play an important role in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis.

CCR3 antagonists are disclosed in WO00/58305.

The present invention provides a pharmaceutical combination comprising a compound of formula (I):



(I)

wherein

Z is CR^4R^5, C(O) or CR^4R^5-Z^1;

Z^1 is C_{1-4} alkylene (such as CH_2), C_{2-4} alkenylene (such as CH=CH) or C(O)NH;

R^1 represents a C_{1-12} alkyl group optionally substituted by one or more substituents independently selected from cyano, hydroxyl, C_{1-6} alkoxy (such as methoxy or ethoxy), C_{1-6} alkylthio (such as methylthio), C_{3-7} cycloalkyl (such as cyclopropyl), C_{1-6} alkoxycarbonyl (such as methoxycarbonyl) and phenyl (itself optionally substituted by one or more of halogen, nitro, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl (such as CF_3), phenyl(C_{1-6} alkyl) (such as benzyl), C_{1-6} alkoxy, C_{1-6} haloalkoxy, $S(O)_2$(C_{1-6} alkyl), $C(O)NH_2$, carboxy or C_{1-6} alkoxycarbonyl); or

R^1 represents C_{2-6} alkenyl optionally substituted by phenyl (itself optionally substituted by one or more of halogen, nitro, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl(C_{1-6} alkyl), C_{1-6} alkoxy, C_{1-6} haloalkoxy, $S(O)_2$(C_{1-6} alkyl), $C(O)NH_2$, carboxy or C_{1-6} alkoxycarbonyl); or

R^1 represents a 3- to 14-membered saturated or unsaturated ring system which optionally comprises up to two ring carbon atoms that form carbonyl groups and which optionally further comprises up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, wherein the ring system is optionally substituted by one or more substituents

independently selected from: halogen, cyano, nitro, oxo, hydroxyl, C_{1-8} alkyl, C_{1-6} hydroxyalkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy(C_{1-6} alkyl), C_{3-7} cycloalkyl(C_{1-6} alkyl), C_{1-6} alkylthio(C_1-C_6 alkyl), C_{1-6} alkylcarbonyloxy(C_{1-6} alkyl), C_{1-6} alkylS(O)$_2$(C_{1-6} alkyl), aryl(C_{1-6} alkyl), heterocyclyl(C_{1-6} alkyl), arylS(O)$_2$(C_{1-6} alkyl), heterocyclylS(O)$_2$(C_{1-6} alkyl), aryl(C_{1-6} alkyl)S(O)$_2$, heterocyclyl(C_{1-6} alkyl)S(O)$_2$, C_{2-6} alkenyl, C_{1-6} alkoxy, carboxy-substituted C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkoxy, C_{1-6} alkylcarboxy-substituted C_{1-6} alkoxy, aryloxy, heterocyclyloxy, C_{1-6} alkylthio, C_{3-7} cycloalkyl(C_{1-6} alkylthio), C_{3-6} alkynylthio, C_{1-6} alkylcarbonylamino, C_{1-6} haloalkylcarbonylamino, SO_3H, NR^7R^8, $C(O)NR^{23}R^{24}$, $S(O)_2NR^{18}R^{19}$, $S(O)_2R^{20}$, $R^{25}C(O)$, carboxyl, C_{1-6} alkoxycarbonyl, aryl and heterocyclyl; wherein the foregoing aryl and heterocyclyl moieties are optionally substituted by one or more of halogen, oxo, hydroxy, nitro, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl(C_{1-6} alkyl), C_{1-6} alkoxy, C_1-C_6 haloalkoxy, S(O)$_2$(C_{1-6} alkyl), $C(O)NH_2$, carboxy or C_{1-6} alkoxycarbonyl;

m is 0 or 1;

Q represents an oxygen or sulphur atom or a group NR^9, C(O), $C(O)NR^9$, $NR^9C(O)$ or CH=CH;

n is 0, 1, 2, 3, 4, 5 or 6 provided that when n is 0, then m is 0;

each R^2 and R^3 independently represents a hydrogen atom or a C_{1-4} alkyl group, or $(CR^2R^3)_n$ represents C_{3-7} cycloalkyl optionally substituted by C_{1-4} alkyl;

T represents a group NR^{10}, $C(O)NR^{10}$, $NR^{11}C(O)NR^{10}$ or $C(O)NR^{10}NR^{11}$;

X^1, X^2, X^3 and X^4 are, independently, CH_2, CHR^{12} {wherein each R^{12} is, independently, C_{1-4} alkyl or C_{3-7} cycloalkyl(C_{1-4} alkyl)} or C=O; or, when they are CHR^{12}, the R^{12} groups of X^1 and X^3 or X^4, or, X^2 and X^3 or X^4 join to form a two or three atom chain which is CH_2CH_2, $CH_2CH_2CH_2$, CH_2OCH_2 or CH_2SCH_2; provided always that at least two of X^1, X^2, X^3 and X^4 are CH_2;

R^4 and R^5 each independently represent a hydrogen atom or a C_1-C_4 alkyl group;

R^6 is aryl or heterocyclyl, both optionally substituted by one or more of: halogen, cyano, nitro, oxo, hydroxyl, C_{1-8} alkyl, C_{1-6} hydroxyalkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy(C_{1-6} alkyl), C_{3-7} cycloalkyl(C_{1-6} alkyl), C_1-C_6 alkylthio(C_{1-6} alkyl), C_{1-6} alkylcarbonyloxy(C_{1-6} alkyl), C_{1-6} alkylS(O)$_2$(C_{1-6} alkyl), aryl(C_{1-6} alkyl), heterocyclyl(C_{1-6} alkyl), arylS(O)$_2$(C_{1-6} alkyl), heterocyclylS(O)$_2$(C_{1-6} alkyl), aryl(C_{1-6} alkyl)S(O)$_2$, heterocyclyl(C_{1-6} alkyl)S(O)$_2$, C_{2-6} alkenyl, C_{1-6} alkoxy, carboxy-substituted C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkoxy,

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C_1-C_6 alkylcarboxy-substituted C_{1-6} alkoxy, aryloxy, heterocyclyloxy, C_{1-6} alkylthio, C_{3-7} cycloalkyl(C_{1-6} alkylthio), C_{3-6} alkynylthio, C_{1-6} alkylcarbonylamino, C_{1-6} haloalkylcarbonylamino, SO_3H, $-NR^{16}R^{17}$, $-C(O)NR^{21}R^{22}$, $S(O)_2NR^{13}R^{14}$, $S(O)_2R^{15}$, $R^{26}C(O)$, carboxyl, C_{1-6} alkoxycarbonyl, aryl and heterocyclyl; wherein the foregoing aryl and heterocyclyl moieties are optionally substituted by one or more of halogen, nitro, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl(C_{1-6} alkyl), C_{1-6} alkoxy, C_{1-6} haloalkoxy, $S(O)_2(C_{1-6}$ alkyl), $C(O)NH_2$, carboxy or C_{1-6} alkoxycarbonyl;

R^7, R^8, R^9, R^{10}, R^{11}, R^{13}, R^{14}, R^{16}, R^{17}, R^{18}, R^{19}, R^{21}, R^{22}, R^{23} and R^{24} are, independently hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-4} alkyl) or phenyl(C_{1-6} alkyl); and,

R^{15} and R^{20} are, independently, C_{1-6} alkyl, C_{1-6} hydroxyalkyl, C_{3-6} cycloalkyl, C_{3-7} cycloalkyl(C_{1-4} alkyl) or C_{1-6} alkyl optionally substituted by phenyl;

R^{25} and R^{26} are, independently, C_{1-6} alkyl or phenyl (optionally substituted by one or more of halogen, nitro, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl(C_{1-6} alkyl), C_{1-6} alkoxy, C_{1-6} haloalkoxy, $S(O)_2(C_{1-6}$ alkyl), $C(O)NH_2$, carboxy or C_{1-6} alkoxycarbonyl);

or a pharmaceutically acceptable salt thereof, or solvate thereof, or a solvate of a salt thereof;

provided that when T is $C(O)NR^{10}$ and R^1 is optionally substituted phenyl then n is not 0;

and a histamine antagonist, a steroid, a leukotriene modulator, a human cytokine, a beta-agonist, a phosphodiesterase inhibitor or an antibody.

Histamine antagonists are, for example, loratidine, desloratidine, fexofenadine, cetirizine, ebastine, astemizole, norastemizole, epinastine or efletirizine.

Steroids are, for example, budesonide, fluticasone, mometasone or rofleponide (such as rofleponide palmitate).

Leukotriene modulators are, for example, montelukast (such as in its sodium salt form), pranlukast, zafirlukast, Z4407 or zafirlukast.

Human cytokines are, for example, recombinant human IL-10 or IL-12.

Beta-agonists are, for example, formoterol, salmeterol or salbutamol.

Phosphodiesterase inhibitors are, for example, SB-207499 (ARIFLO®) or theophylline.

Antibodies are, for example, anti-IL-5 antibodies or anti-TNF-antibodies (such as infliximab).

Certai: mpounds of formula (I) are capable of existing in isomeric forms (for example as tautomers, enantiomers, geometric isomers or diastereomers). The present invention encompasses all such isomers and mixtures thereof in all proportions.

Hydroxyalkyl is, for example, 2-hydroxyeth-1-yl. Haloalkyl is, for example, CF_3. Alkoxy is, for example, methoxy or ethoxy. Alkoxy(C_{1-6} alkyl) is, for example, methoxymethyl or ethoxyethyl. Cycloalkyl is, for example, cyclopropyl or cyclohexyl. Cycloalkyl(C_{1-6} alkyl) is, for example, cyclopropylmethyl. Alkylthio is, for example, methylthio or ethylthio. Alkylthio(C_{1-6} alkyl) is, for example, methylthiomethyl. Alkylcarbonyloxy(C_{1-6} alkyl) is, for example, $CH_3C(O)OCH_2$. $S(O)_2$(C_{1-6} alkyl) is, for example, $CH_3S(O)_2$. Alkyl$S(O)_2$(C_{1-6} alkyl) is, for example, $CH_3S(O)_2CH_2$. Aryl(C_{1-6} alkyl) is, for example, benzyl, 2-phenyleth-1-yl or 1-phenyleth-1-yl. Heterocyclyl(C_{1-6} alkyl) is, for example, heterocyclylmethyl. Aryl$S(O)_2$(C_{1-6} alkyl) is, for example, phenyl$S(O)_2CH_2$. Heterocyclyl$S(O)_2$(C_{1-6} alkyl) is, for example, heterocyclyl$S(O)_2CH_2$. Aryl(C_{1-6} alkyl)$S(O)_2$ is, for example, benzyl$S(O)_2$. Heterocyclyl(C_{1-6} alkyl)$S(O)_2$ is, for example, heterocyclyl$CH_2S(O)_2$. Alkenyl is, for example, vinyl or allyl. Carboxy-substituted C_{1-6} alkoxy is, for example, $HOC(O)CH_2CH_2O$. Haloalkoxy is, for example, OCF_3. Hydroxyalkoxy is, for example, $HOCH_2CH_2O$. Alkylcarboxy-substituted C_{1-6} alkoxy is, for example, $CH_3OC(O)CH_2CH_2O$. Aryloxy is, for example, phenoxy. Heterocyclyloxy is, for example, pyridinyloxy or pyrimidinyloxy. C_{3-7} cycloalkyl(C_{3-6} alkylthio) is, for example, cyclopropylCH_2S. Alkynylthio is, for example, propargylthio. Alkylcarbonylamino is, for example, acylamino. Haloalkylcarbonylamino is, for example, $ClCH_2C(O)NH$. Alkoxycarbonyl is, for example, $CH_3OC(O)$.

Aryl is a carbocyclic aromatic ring optionally fused to one or more carbocyclic rings. Aryl is, for example, phenyl, naphthyl or indanyl.

Heterocyclyl is an aromatic or non-aromatic ring system preferably comprising up to 6 (preferably up to 4) heteroatoms selected from the group comprising nitrogen, oxygen and sulphur, and preferably comprising one, two or three 5- or 6-membered rings. Heterocyclyl is, for example, furyl, thienyl, pyrrolyl, 2,5-dihydropyrrolyl, thiazolyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, pyridinyl (for example 2-pyridinyl, 3-pyridinyl or 4-pyridinyl), pyrimidinyl (for example 2-pyrimidinyl or 4-pyrimidinyl), pyrazinyl, pyridazinyl, indolyl, 2,3-dihydroindolyl,

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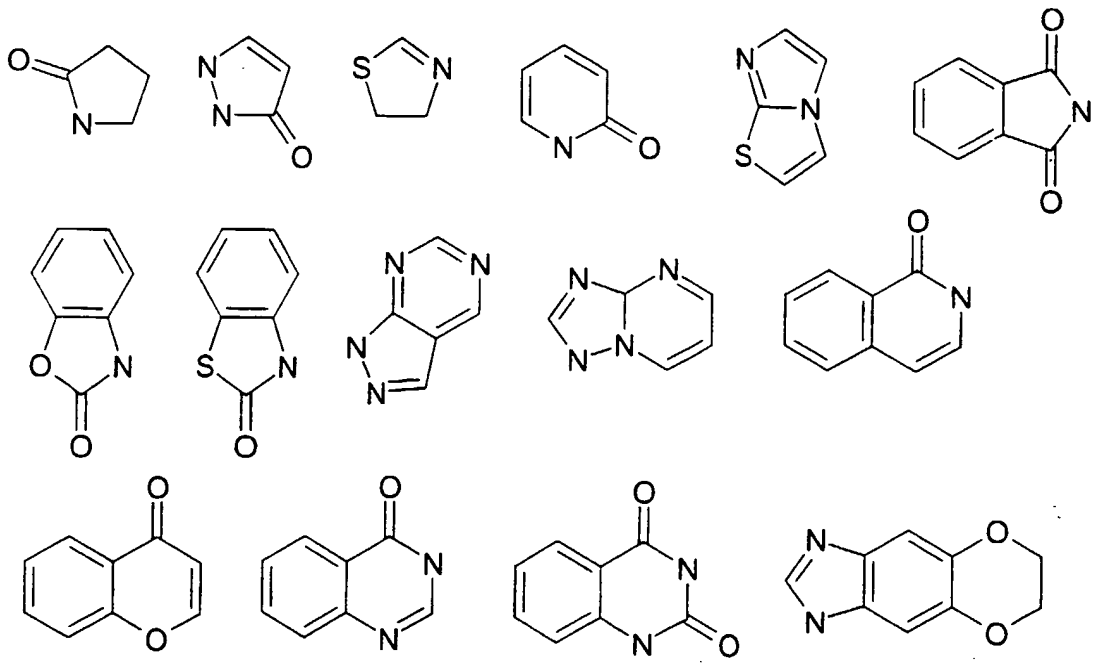
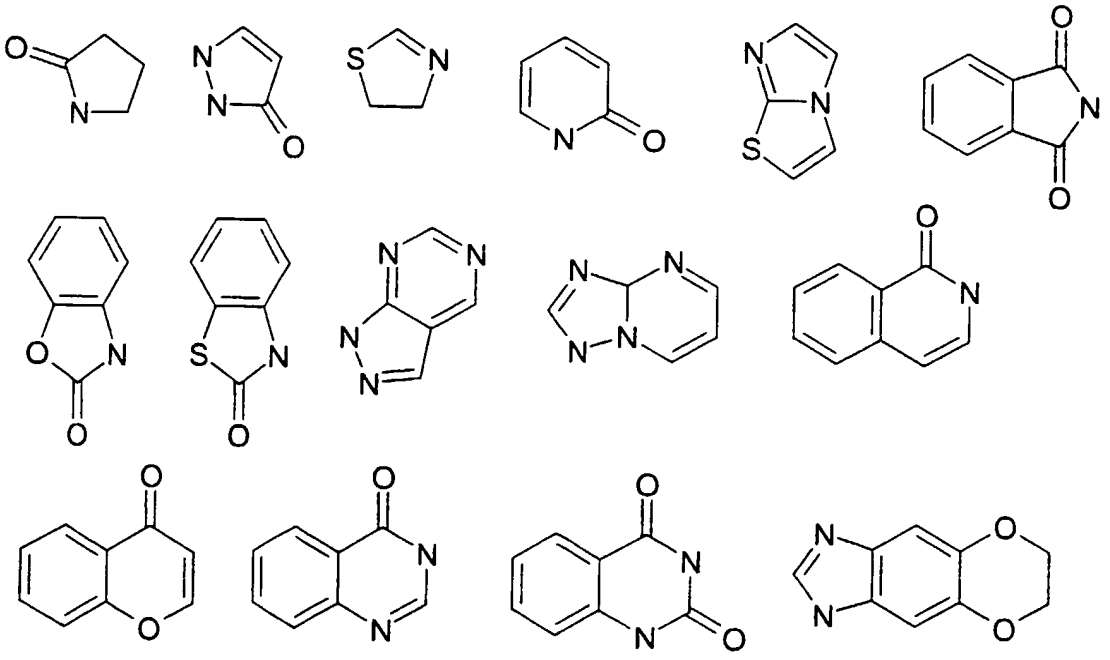
benzo[b]furyl, benz[b]thienyl, 2,3-dihydrobenz[b]thienyl (for example 1-dioxo-2,3-dihydrobenz[b]thienyl), benzimidazolyl, benztriazolyl, benzoxazolyl, benzthiazolyl, 2,3-dihydrobenzthiazolyl (for example 2,3-dihydrobenzthiazol-2-onyl which is also known as 2-oxo-1,3-benzothiazol-3(2H)-yl), 1,2,3-benzothiadiazolyl, 1,2,3-benzoxadiazolyl, 2,1,3-benzothiadiazolyl, 2,1,3-benzoxadiazolyl, quinoxalinyl, dihydro-1-benzopyryliumyl (for example a coumarinyl or a chromenonyl), 1,3-benzodioxolyl (also known as 1,2-methylenedioxyphenyl), 3,4-dihydro-1H-2,1-benzothiazinyl (for example 2-dioxo-3,4-dihydro-1H-2,1-benzothiazinyl), purine (for example 1H-purine or 9H-purine), 1H-pyrazolo[3,4-d]pyrimidinyl, thieno[2,3-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, quinolinyl (for example 2-quinolinyl, 3-quinolinyl or 4-quinolinyl), isoquinolinyl, quinazolinyl or dibenzothiophenyl; or a ring as shown below:



The group R^1 may represent an optionally substituted 3- to 14-membered (especially 5- to 10-membered) saturated or unsaturated ring system which optionally comprises one or two ring carbon atoms that form carbonyl groups and which optionally further comprises one, two, three or four ring heteroatoms independently selected from nitrogen, oxygen and sulphur. Examples of R^1 ring systems, which can be moncyclic or polycyclic, include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, indanyl, furyl, thienyl, pyrrolyl, 2,5-dihydropyrrolyl, thiazolyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl,

tetrazolyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, pyridinyl (for example 2-pyridinyl, 3-pyridinyl or 4-pyridinyl), pyrimidinyl (for example 2-pyrimidinyl or 4-pyrimidinyl), pyrazinyl, pyridazinyl, indolyl, 2,3-dihydroindolyl, benzo[b]furyl, benz[b]thienyl, 2,3-dihydrobenz[b]thienyl (for example 1-dioxo-2,3-dihydrobenz[b]thienyl), benzimidazolyl, benztriazolyl, benzoxazolyl, benzthiazolyl, 2,3-dihydrobenzthiazolyl (for example 2,3-dihydrobenzthiazol-2-onyl which is also known as 2-oxo-1,3-benzothiazol-3(2H)-yl), 1,2,3-benzothiadiazolyl, 1,2,3-benzoxadiazolyl, 2,1,3-benzothiadiazolyl, 2,1,3-benzoxadiazolyl, quinoxalinyl, dihydro-1-benzopyryliumyl (for example a coumarinyl or a chromenonyl), 1,3-benzodioxolyl (also known as 1,2-methylenedioxyphenyl), 3,4-dihydro-1H-2,1-benzothiazinyl (for example 2-dioxo-3,4-dihydro-1H-2,1-benzothiazinyl), purine (for example 1H-purine or 9H-purine), 1H-pyrazolo[3,4-d]pyrimidinyl, thieno[2,3-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, quinolinyl (for example 2-quinolinyl, 3-quinolinyl or 4-quinolinyl), isoquinolinyl, quinazolinyl or dibenzothiophenyl; or a ring as shown below:

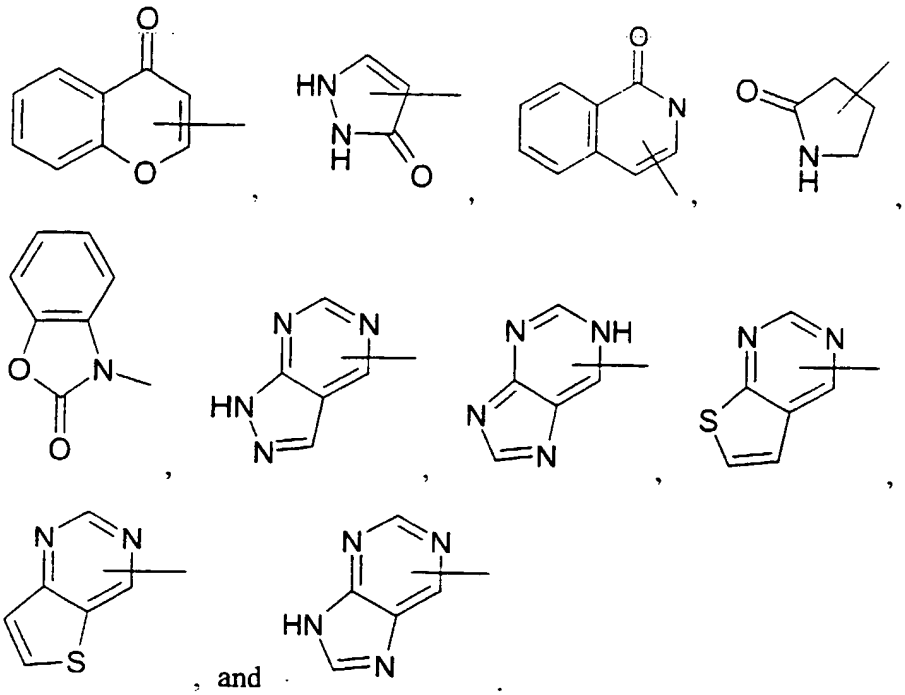


Alkyl may be linear or branched. Examples of alkyl groups/moieties containing up to twelve carbon atoms include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-undecyl and n-dodecyl groups. A C_{1-6} hydroxyalkyl group will comprise at least one hydroxyl group (for example one, two or three hydroxyl groups) which may be attached to an internal or terminal carbon

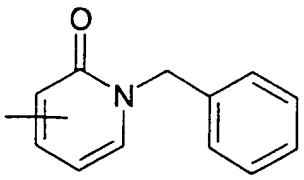
atom of the alkyl chain. Similarly, a carboxy-substituted C_{1-6} alkoxy group will comprise at least one carboxyl group (for example one, two or three carboxyl groups) which may be attached to an internal or terminal carbon atom of the alkyl chain. A C_{1-6} haloalkyl or C_{1-6} haloalkoxy group will comprise at least one halogen atom (for example one, two, three or four halogen atoms independently selected from fluorine, chlorine, bromine and iodine) which may be attached to an internal or terminal carbon atom of the alkyl chain. A halophenyl group will comprise from 1 to 5 halogen atoms independently selected from fluorine, chlorine, bromine and iodine. A C_{1-6} alkylbenzyl group will comprise at least one C_{1-6} alkyl group (for example one, two or three C_{1-6} alkyl groups) attached to the phenyl ring of the benzyl moiety. If there is more than one C_{1-6} alkyl group attached to the phenyl ring, the groups may be the same or different. In a C_{1-6} alkoxycarbonylpiperazinyl substituent group, the piperazinyl moiety is attached through a nitrogen atom to the carbonyl moiety. When T represents $C(O)NR^9$, it should be understood that the nitrogen atom is attached directly to the six-membered heterocyclic ring in formula (I).

The group R^1 may represent a C_{1-12}, preferably C_{1-10}, more preferably C_{1-6}, alkyl group optionally substituted by one or more (for example one, two, three or four) substituents independently selected from cyano, hydroxyl, C_{1-6}, preferably C_{1-4}, alkoxy, C_{1-6}, preferably C_{1-4}, alkylthio and C_{1-6} alkoxycarbonyl, preferably C_{1-4} alkoxycarbonyl.

The group R^1 may alternatively represent an optionally substituted 3- to 10-membered saturated or unsaturated ring system which optionally comprises one or two ring carbon atoms that form carbonyl groups and which optionally further comprises one, two, three or four ring heteroatoms independently selected from nitrogen, oxygen and sulphur. Examples of ring systems that may be used which can be moncyclic or polycyclic include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, pyrazolyl, furyl, thienyl, imidazolyl, quinolinyl (for example 2-quinolinyl, 3-quinolinyl or 4-quinolinyl), pyridinyl (for example 2-pyridinyl, 3-pyridinyl or 4-pyridinyl), 1,3-benzodioxolyl, thiazolyl, benzimidazolyl, oxadiazolyl (for example 1,2,4-oxadiazolyl), triazolyl (such as 1,2,3-triazolyl or 1,2,4-triazolyl), benzothiazolyl, pyrimidinyl (for example 2-pyrimidinyl or 4-pyrimidinyl), benzothienyl,



The ring system of R^1 may be optionally substituted by one or more (for example one, two, three or four) substituents independently selected from halogen (for example fluorine, chlorine, bromine or iodine); cyano; nitro; hydroxyl; carboxyl; C_{1-6}, preferably C_{1-4}, alkyl (especially methyl or ethyl); C_{1-6}, preferably C_{1-4}, hydroxyalkyl; C_{1-6}, preferably C_{1-4}, haloalkyl (for example trifluoromethyl); C_{1-6}, preferably C_{1-4}, alkoxy (especially methoxy, ethoxy, n-propoxy or isopropoxy); carboxy-substituted C_{1-6}, preferably C_{1-4}, alkoxy; C_{1-6}, preferably C_{1-4}, alkylthio (especially methylthio, ethylthio, n-propylthio and tert-butylthio); C_{1-6}, preferably C_{1-4}, alkylthiomethyl (particularly methylthiomethyl); C_{1-6}, preferably C_{1-4}, alkylcarbonylamino (especially methylcarbonylamino); $-NR^7R^8$; $-C(O)NR^7R^8$; C_{1-6}, preferably C_{1-4}, alkylcarbonyloxymethyl (particularly methylcarbonyloxymethyl); C_{1-6}, preferably C_{1-4}, alkoxycarbonyl (especially methoxycarbonyl or ethoxycarbonyl); C_{1-6}, preferably C_{1-4}, alkoxycarbonylpiperazinyl; furyl; phenyl; pyridinyl; pyrazinyl; halophenyl (especially chlorophenyl); thienyl; thienylmethyl; C_{1-6}, preferably C_{1-4}, alkylbenzyl (particularly methylbenzyl); and



The group R^1 may be an aromatic 5-membered heterocyclyl having 2, 3 or 4 ring nitrogen atoms (for example 1,2,4-triazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole or tetrazole) substituted by one heteroaromatic ring (such as pyridine or pyrazole) which is itself optionally substituted by halogen or C_{1-4} alkyl; or R^1 is halophenyl (for example phenyl optionally substituted (such as in the 4-position) by fluoro or chloro; such as 4-chlorophenyl or 4-fluorophenyl).

The group Q is especially oxygen or m is 0. Alternatively, Q may be a sulphur atom or a group NH, C(O) or NHC(O).

The group n is, for example, 1 or 2.

The group T is, for example, NH, C(O)NH or NHC(O)NH; for example T is a NH or C(O)NH group; especially T is C(O)NH.

The groups X^1, X^2, X^3 and X^4 are preferably all CH_2 or CHR^{12}, wherein the R^{12} groups of X^1 and X^3 or X^4, or, X^2 and X^3 or X^4 join to form CH_2CH_2; provided always that at least two of X^1, X^2, X^3 and X^4 are CH_2. The groups X^1, X^2, X^3 and X^4 are especially all CH_2.

It is preferred that each R^2 and R^3 independently represents a hydrogen atom or a methyl group, especially a hydrogen atom.

The groups R^4 and R^5 are especially, independently, hydrogen or C_{1-4} alkyl; particularly both hydrogen.

The group R^6 is, for example, a phenyl group optionally substituted by one or more (for example one, two, three or four) substituents independently selected from halogen (for example fluorine, chlorine, bromine or iodine), amino, nitro, cyano, sulphonyl, sulphonamido, C_{1-6}, preferably C_{1-4}, alkyl, C_{1-6}, preferably C_{1-4}, haloalkoxy, methylenedioxy or C_{1-6}, preferably C_{1-4}, alkylsulphonyl. The group R^6 is especially phenyl optionally substituted by halogen or methylenedioxy, particularly R^6 is a phenyl group substituted by halogen. Examples of R^6 include 3-chlorophenyl, 4-chlorophenyl or, especially, 3,4-dichlorophenyl.

The groups R^7 and R^8 are, for example, hydrogen, C_1-C_6, preferably C_1-C_4, hydroxyalkyl, C_{3-6} cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl) or C_{1-6}, preferably C_{1-4}, alkyl optionally substituted by phenyl (for example one or two phenyl groups). More preferably, R^7 and R^8 each independently represent hydrogen, C_2 hydroxyalkyl, cyclopropyl or C_{1-2} alkyl optionally substituted by phenyl.

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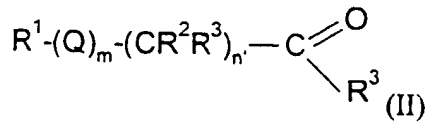
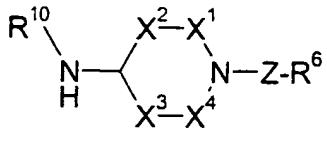
Compounds of formula (I) can be prepared by one of the following methods:

(a) when n is at least 1, the CR^2R^3 group attached directly to T is CHR^3 and T is NR^{10}, reacting a compound of formula



(II)

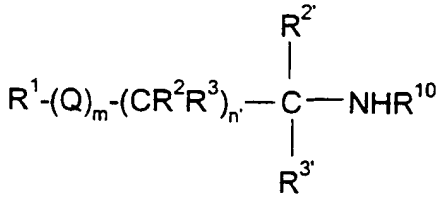
wherein n' is 0 or an integer from 1 to 3 and R^1, R^2, R^3, m and Q are as defined above, with a compound of formula



(III)

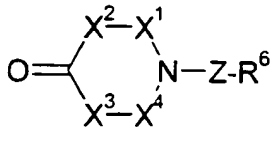
or a salt thereof, wherein X^1, X^2, X^3, X^4, Z, R^6 and R^{10} are as defined above, in the presence of a reducing agent;

(b) when n is at least 1, the CR^2R^3 group attached directly to T is $C(C_1\text{-}C_4\ alkyl)_2$ and T is NR^{10}, reacting a compound of formula



(IV)

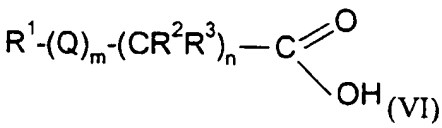
wherein n' is 0 or an integer from 1 to 3, $R^{2'}$ and $R^{3'}$ each independently represent a $C_1\text{-}C_4$ alkyl group, and R^1, R^2, R^3, R^{10}, m and Q are as defined above, with a compound of formula



(V)

wherein X^1, X^2, X^3, X^4, Z and R^6 are as defined above, in the presence of a reducing agent;

(c) when T is $C(O)NR^{10}$, reacting a compound of formula



(VI)

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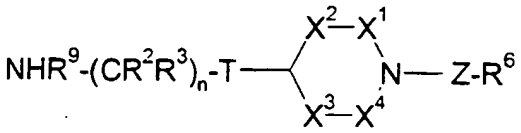
wherein R^1, R^2, R^3, Q, m and n are as defined above, with a compound of formula (III) or a salt thereof as defined in (a) above;

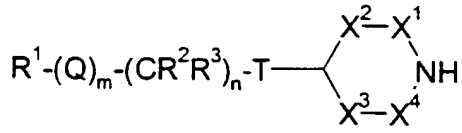
(d) when m is 1 and Q is NR^9, reacting a compound of formula (VII), R^1 - L^1, wherein L^1 represents a leaving group (for example a halogen atom) and R^1 is as defined above, with a compound of formula



(VIII)

or a salt thereof, wherein n, T, X^1, X^2, X^3, X^4, Z, R^2, R^3, R^6 and R^9 are as defined above;

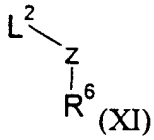
(e) when at least one of R^4 and R^5 represents a hydrogen atom, reacting a compound of formula



(IX)

or a salt thereof, wherein R^1, R^2, R^3, Q, m, n, X^1, X^2, X^3, X^4 and T are as defined above, with a compound of general formula (X), R^6 - C(O) - R^{20}, wherein R^{20} represents a hydrogen atom or a C_1-C_4 alkyl group and R^6 is as defined above, in the presence of a reducing agent;

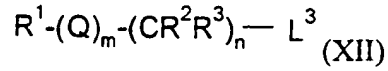
(f) reacting a compound of formula (IX) as defined in (e) above, with a compound of formula



(XI)

wherein L^2 represents a leaving group (for example a halogen atom) and Z and R^6 are as defined above;

(g) when T is NR^{10}, reacting a compound of formula



(XII)

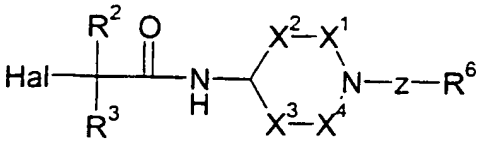
wherein L^3 represents a leaving group (for example a halogen atom) and R^1, R^2, R^3, m, n and Q are as defined above, with a compound of formula (III) or a salt thereof as defined in (a) above;

(h) when T is $NHC(O)NR^{10}$, reacting a compound of formula

$$R^1\text{-}(Q)_m\text{-}(CR^2R^3)_n\text{—}\ N{=}C{=}O \qquad \text{(XIII)}$$

wherein R^1, R^2, R^3, Q, m and n are as defined above, with a compound of formula (III) or a salt thereof as defined in (a) above;

(i) when T is C(O)NH, Z is CH_2, n is 1, R^2 and R^3 are hydrogen or C_1-C_4 alkyl and Q is oxygen or sulphur, reacting a compound of formula (XIV):



(XIV)

wherein Hal is a suitable halogen (such as bromo or chloro), R^2, R^3, X^1, X^2, X^3, X^4, Z and R^6 are as defined above, with R^1OH or R^1SH in the presence of a suitable base (such as potassium carbonate or sodium or potassium hydroxide);

and optionally after (a), (b), (c), (d), (e), (f), (g), (h) or (i) forming a pharmaceutically acceptable salt or solvate of the compound of formula (I) obtained. Compounds of formulae (II) to (XIV) are either commercially available, or are known in the literature or may be prepared using known techniques. The compounds of formula (I) can be isolated from reaction mixtures and purified using standard techniques.

When functional groups such as hydroxyl or amino are present in starting reagents or intermediate compounds they may need to be protected by protecting groups. Thus, the preparation of the compounds of formula (I) may involve, at an appropriate stage, the addition and subsequent removal of one or more protecting groups. The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of chemokine receptor activity, especially as modulators of the activity of the CCR3 chemokine receptor.

The pharmaceutical combination of the present invention can be used to in the treatment of conditions or diseases in which both antagonism of CCR3 chemokine receptor activity and histamine antagonism, leukotriene modulation, beta-agonism,

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phosphodiesterase inhibition or the administration of a steroid, human cytokine or an antibody is beneficial. Examples of these conditions include:

(1) **(the respiratory tract)** obstructive airways diseases including chronic obstructive pulmonary disease (COPD); asthma, such as bronchial, allergic, intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma (for example late asthma and airways hyper-responsiveness); bronchitis; acute, allergic, atrophic rhinitis and chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca and rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous and pseudomembranous rhinitis and scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) and vasomotor rhinitis; sarcoidosis, farmer's lung and related diseases, fibroid lung and idiopathic interstitial pneumonia;

(2) **(skin)** psoriasis, atopical dermatitis, contact dermatitis and other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythemas, cutaneous eosinophilias, uveitis, Alopecia areata and conjunctivitis (for example vernal conjunctivitis);

(3) **(gastrointestinal tract)** Coeliac disease, proctitis, eosinopilic gastro-enteritis, mastocytosis, Crohn's disease, inflammatory bowel disease, irritable bowel syndrome, ulcerative colitis, food-related allergies which have effects remote from the gut, for example, migraine, rhinitis and eczema;

(4) **(bone and joints)** rheumatoid arthritis, osteoarthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome and systemic sclerosis;

(5) **(allograft rejection)** acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease; and,

(6) **(other tissues and systemic disease)** multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus, systemic lupus, erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, sezary syndrome and idiopathic thrombocytopenia pupura.

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Thus, the present invention provides a pnarmaceutical combination as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a pharmaceutical combination as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the disease or condition in question. Persons at risk of developing a particular disease or condition generally include those having a family history of the disease or condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the disease or condition.

In another aspect the present invention provides the use of a pharmaceutical combination as hereinbefore defined in the manufacture of a medicament for the modulation of the CCR3 chemokine receptor and histamine antagonism, leukotriene modulation, beta-agonism, phosphodiesterase inhibition or the administration of a steroid, human cytokine or an antibody is beneficial. In a further aspect such medicament is for the treatment of asthma or rhinitis.

The invention also provides a method of treating asthma or rhinitis in a person suffering from, or at risk of, said disease, which comprises administering to the person a therapeutically effective amount of a pharmaceutical combination as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

The compound of formula (I) and the histamine antagonist, steroid, leukotriene modulator, human cytokine, beta-agonist, phosphodiesterase inhibitor or antibody may be comprised in the same or separate formulations. When in separate formulations, the compound of formula (I) may be administered before, at or about the same time as or after the histamine antagonist, steroid, leukotriene modulator, human cytokine, beta-agonist, phosphodiesterase inhibitor or antibody.

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In one further aspect of the invention the compound of formula (I) is administered at or about the same time as the histamine antagonist, steroid, leukotriene modulator, human cytokine, beta-agonist, phosphodiesterase inhibitor or antibody. Especially, the compound of formula (I) and the histamine antagonist, steroid, leukotriene modulator, human cytokine, beta-agonist, phosphodiesterase inhibitor or antibody. Further, said formulation is designed for oral administration.

In a further aspect the present invention provides a pharmaceutical composition comprising a compound of formula (I) and a histamine antagonist, steroid, leukotriene modulator, human cytokine, beta-agonist, phosphodiesterase inhibitor or antibody and a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99%w (per cent by weight), more preferably from 0.05 to 80%w, still more preferably from 0.10 to 70%w, and even more preferably from 0.10 to 50%w, of active ingredients, all percentages by weight being based on total composition.

The pharmaceutical composition may be administered topically (for example to the lung and/or airways or to the skin) in the form of a solution, suspension, heptafluoroalkane aerosol or dry powder formulation; or systemically, for example by oral administration in the form of a tablet, capsule, syrup, powder, aerosol or granule, or by parenteral administration in the form of a solution or suspension, or by subcutaneous administration or by rectal administration in the form of a suppository or transdermally.

The combination may be formulated as a tablet which may include a diluent such as microcrystalline cellulose or lactose monohydrate, a binder such as polyvinylpyrrolidone or hydroxypropylmethylcellulose, a disintegrant such as crospovidone or starch, a glidant such as talc or fumed silica and a lubricant such as magnesium stearate or sodium stearyl fumarate. Optionally, an excipient to control the release rate of the active compounds, such as hydroxypropylmethylcellulose or polymethylmethacrylate derivatives, may be included.

Alternatively, the formulation may be presented as a capsule with either a gelatin, starch or hydroxypropylmethylcellulose shell and a fill formulation comprising the active ingredients and a diluent such as microcrystalline cellulose or lactose monohydrate, a binder such as polyvinylpyrrolidone or hydroxypropylmethylcellulose, a disintegrant such as crospovidone or starch, a glidant such as talc or fumed silica, and a lubricant such as

magnesium stearate or sodium stearyl fumarate. Optionally, an excipient to control the release rate of the active compounds, such as hydroxypropylmethylcellulose or polymethylmethacrylate derivatives, may be included.

Parenteral dosage forms may be prepared using an aqueous or organic vehicle, such as oils, alcohols, propylene glycol, polyethylene glycol or other pharmaceutically acceptable solvent, solubilisers such as polyethylene oxide - polypropylene oxide block copolymers or polysorbates, tonicity modifiers such as sodium chloride or dextrose, stabilisers such as antixoidants or chelating agents, and pH modifiers and buffers such as sodium hydroxide or sodium borate.

Oral dosage forms can be prepared by tabletting or encapsulation of blends produced by wet granulation, dry granulation, print deposition, direct powder blending or other pharmaceutically acceptable process.

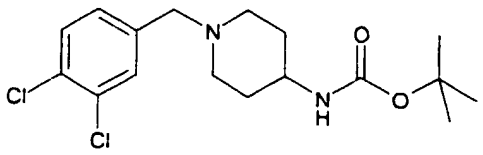
Parenteral dosage forms may be prepared by processes such as preparation of a solution, colloid, suspension or emulsion which is then sterilised, by processes such as filtration, autoclaving or irradiation. The dosage form may also be presented as a lyophilised solid for reconstitution.

The following Examples illustrate processes by which compounds of formula (I) can be prepared.

EXAMPLE A

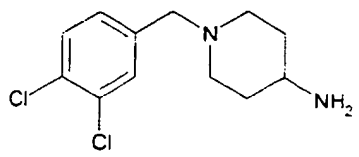
Preparation of 1-(3,4-dichlorobenzyl)-4-piperidinamine, di-trifluoroacetate salt

Step i: tert-butyl 1-(3,4-dichlorobenzyl)-4-piperidinylcarbamate



Sodium triacetoxyborohydride (6g) was added to a stirred solution of 3,4-dichlorobenzaldehyde (4.2g) and 1,1-dimethylethyl-4-piperidinyl carbamate (4g) in dichloromethane (50ml). The mixture was stirred at room temperature for 4h then partitioned between ethyl acetate and aqueous sodium hydrogencarbonate. The organic layer was washed with water, dried and evaporated under reduced pressure. The residue was triturated with ether to give a white solid (3.5g) which was used directly in step ii.

Step ii: 1-(3,4-Dichlorobenzyl)-4-piperidinamine, di-trifluoroacetate salt



$2CF_3CO_2H$

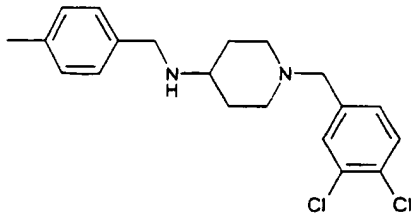
The product from step (i) (3.5g) was treated with trifluoroacetic acid (10ml) in dichloromethane (40ml). After 72h, the solution was evaporated, the residue triturated with ether and the solid (4.3g) collected.

Examples 1-47

1-(3,4-Dichlorobenzyl)-4-piperidinamine, di-trifluoroacetate salt (2mg), the appropriate aldehyde (2 equivalents), sodium triacetoxyborohydride (3 equivalents) and diisopropylethylamine (2 equivalents) in acetonitrile (0.08ml) and 1-methyl-2-pyrrolidinone (0.12ml) were left at room temperature for 24h. The reaction mixture was evaporated to dryness and the residue dissolved in dimethylsuphoxide (0.4ml).

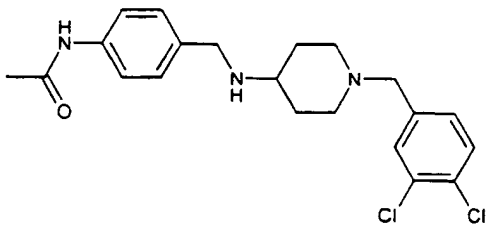
Example 1

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-methylbenzyl)amine



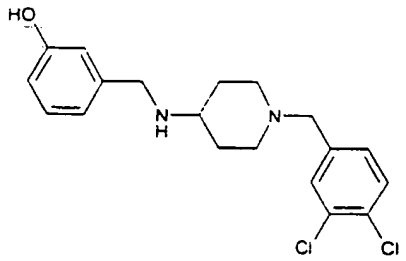
Example 2

N-[4-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)phenyl]acetamide



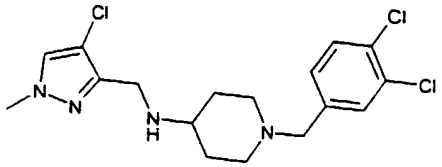
Example 3

3-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)phenol



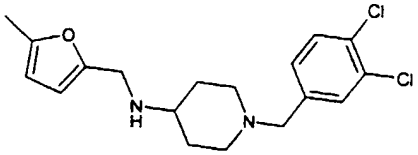
Example 4

N-[(4-Chloro-1-methyl-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine.



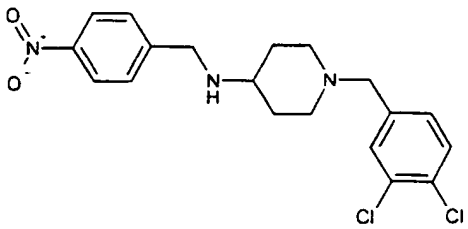
Example 5

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(5-methyl-2-furyl)methyl]amine



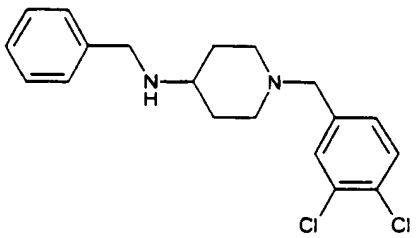
Example 6

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-nitrobenzyl)amine



Example 7

N-Benzyl-1-(3,4-dichlorobenzyl)-4-piperidinamine



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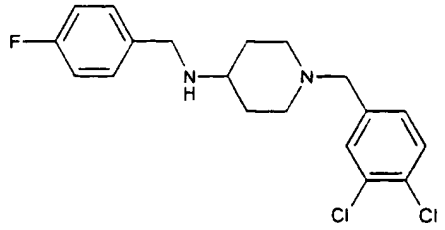
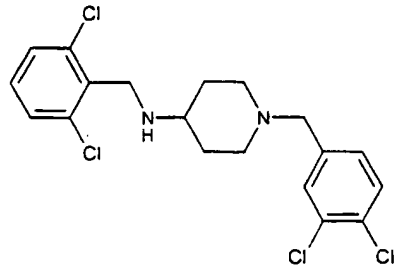
Example 8

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-fluorobenzyl)amine



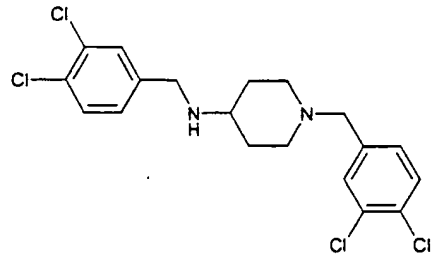
Example 9

N-(2,6-Dichlorobenzyl)-1-(3,4-dichlorobenzyl)-4-piperidinamine



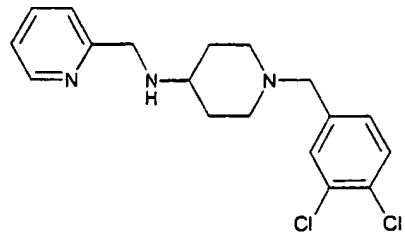
Example 10

N,1-Bis(3,4-dichlorobenzyl)-4-piperidinamine



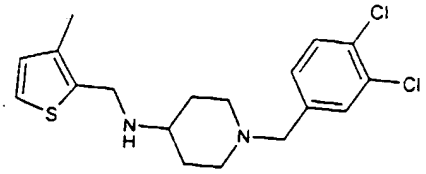
Example 11

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(2-pyridinylmethyl)amine



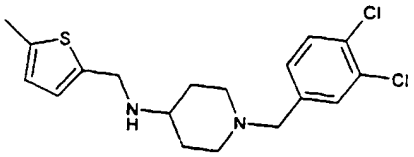
Example 12

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(3-methyl-2-thienyl)methyl]amine



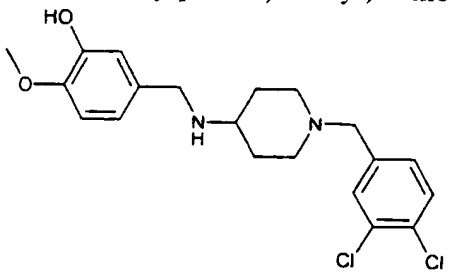
Example 13

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(5-methyl-2-thienyl)methyl]amine



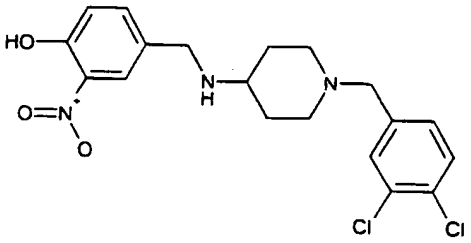
Example 14

5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-methoxyphenol



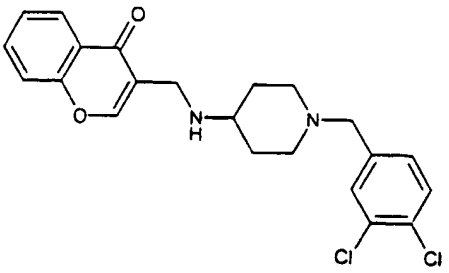
Example 15

4-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-nitrophenol



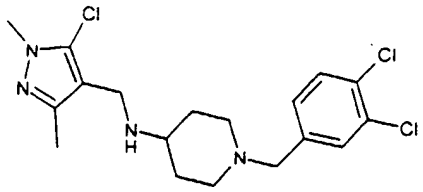
Example 16

3-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-4H-chromen-4-one



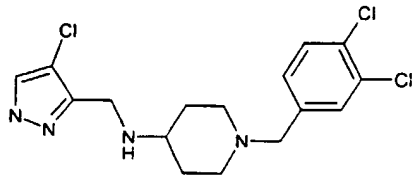
Example 17

N-[(5-Chloro-1,3-dimethyl-1H-pyrazol-4-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine



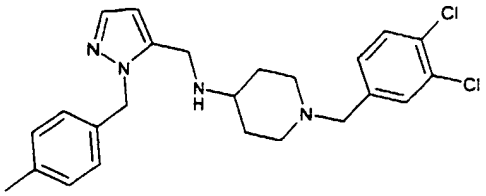
Example 18

N-[(4-Chloro-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine



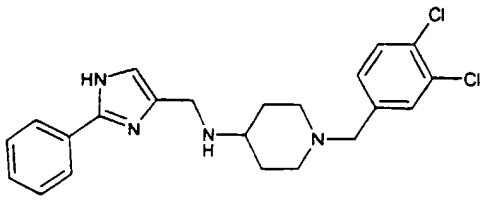
Example 19

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-{[1-(4-methylbenzyl)-1H-pyrazol-5-yl]methyl}amine



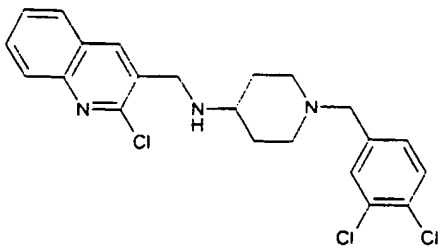
Example 20

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(2-phenyl-1H-imidazol-4-yl)methyl]amine



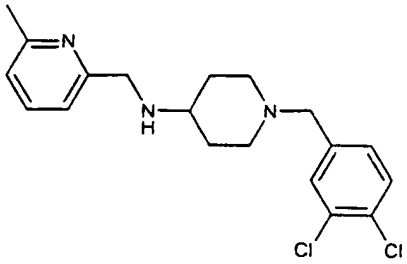
Example 21

N-[(2-Chloro-3-quinolinyl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine



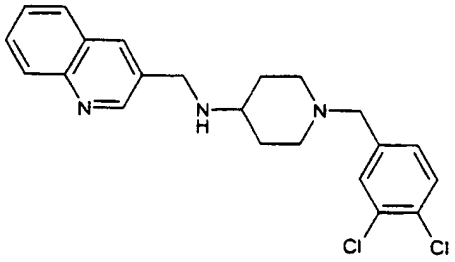
Example 22

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(6-methyl-2-pyridinyl)methyl]amine



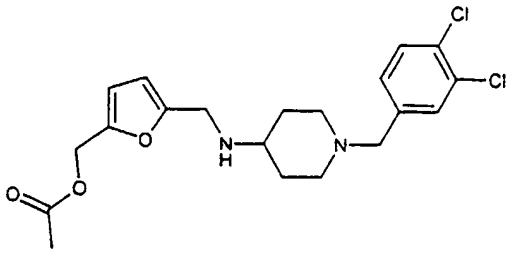
Example 23

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(3-quinolinylmethyl)amine



Example 24

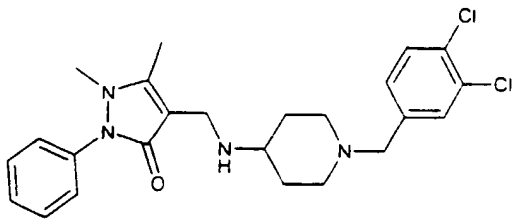
[5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-furyl]methyl acetate



Example 25

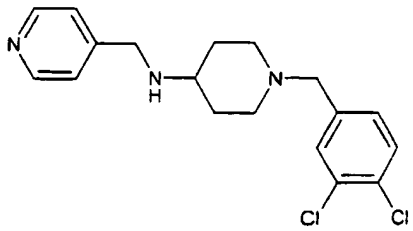
4-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one

BNSDOCID: <GB_ _2373186A_I_>



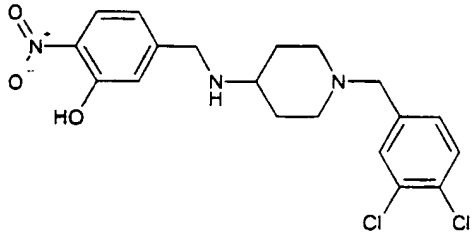
Example 26

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-pyridinylmethyl)amine



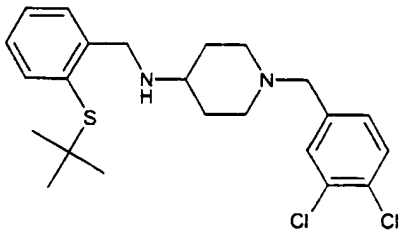
Example 27

5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-nitrophenol



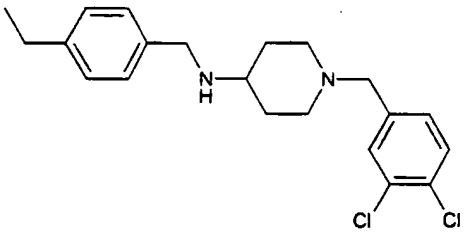
Example 28

N-[2-(tert-Butylsulfanyl)benzyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine



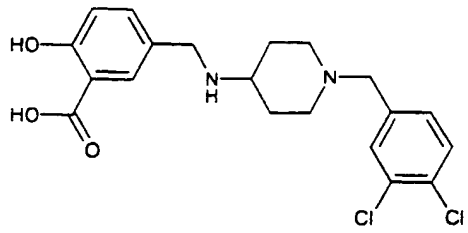
Example 29

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-ethylbenzyl)amine



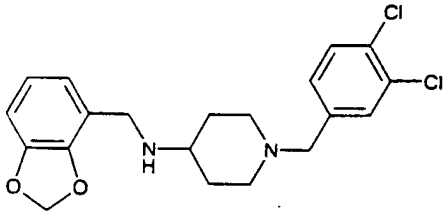
Example 30

5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-hydroxybenzoic acid



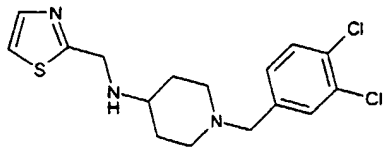
Example 31

N-(1,3-Benzodioxol-4-ylmethyl)-1-(3,4-dichlorobenzyl)-4-piperidinamine



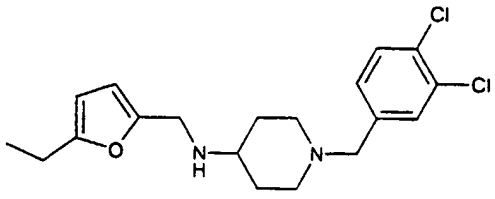
Example 32

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(1,3-thiazol-2-ylmethyl)amine



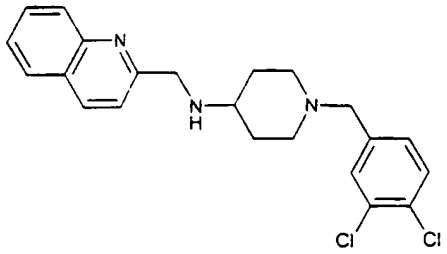
Example 33

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(5-ethyl-2-furyl)methyl]amine



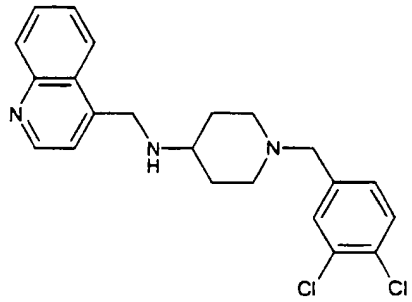
Example 34

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(2-quinolinylmethyl)amine



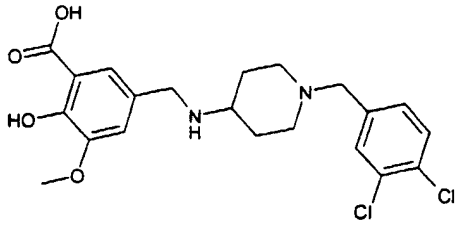
Example 35

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-quinolinylmethyl)amine



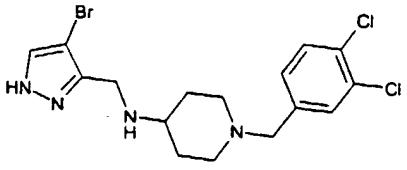
Example 36

5-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-hydroxy-3-methoxybenzoic acid



Example 37

N-[(4-Bromo-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine



Example 38

2-[2-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-6-methoxyphenoxy]acetic acid

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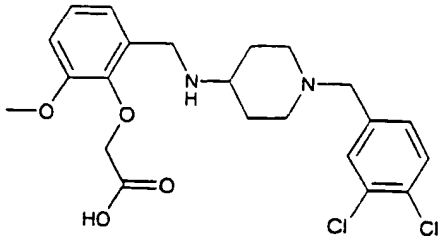
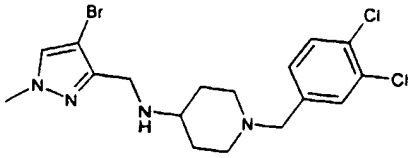


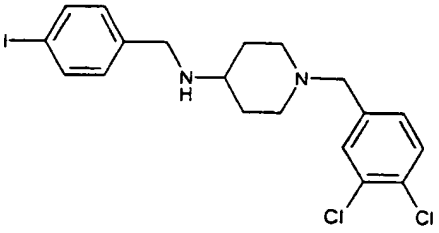
Example 39

N-[(4-Bromo-1-methyl-1H-pyrazol-3-yl)methyl]-1-(3,4-dichlorobenzyl)-4-piperidinamine



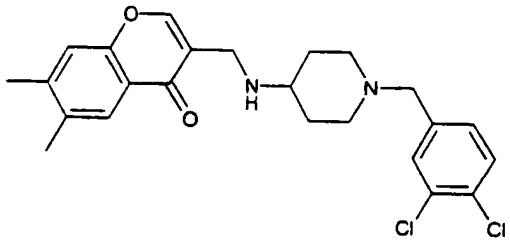
Example 40

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-iodobenzyl)amine



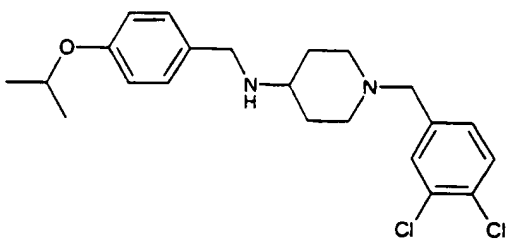
Example 41

3-({[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}methyl)-6,7-dimethyl-4H-chromen-4-one



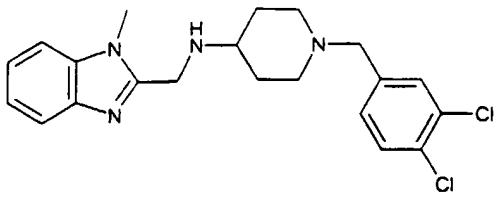
Example 42

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-isopropoxybenzyl)amine



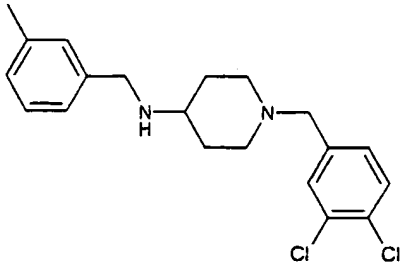
Example 43

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-[(1-methyl-1H-benzimidazol-2-yl)methyl]amine



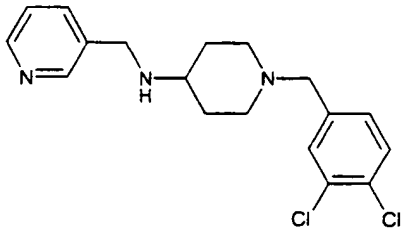
Example 44

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(3-methylbenzyl)amine



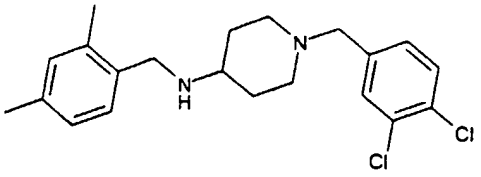
Example 45

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(3-pyridinylmethyl)amine



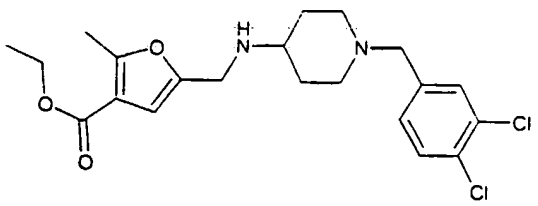
Example 46

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(2,4-dimethylbenzyl)amine



Example 47

Ethyl 5-({[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}methyl)-2-methyl-3-furoate

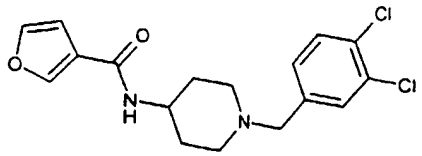


Examples 48-73

Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (2 equiv) was added to a solution of 1-(3,4-dichlorobenzyl)-4-piperidinamine, di-hydrochloride salt (1mg), the appropriate acid (2 equivalents) and diisopropylethylamine (5 equivalents) in dimethylformamide (0.17ml) and was left at room temperature for 24h. The reaction mixture was evaporated to dryness and the residue dissolved in dimethylsulphoxide (0.3ml).

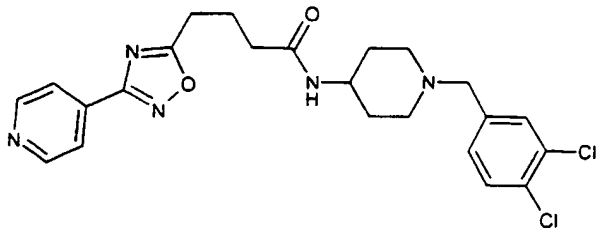
Example 48

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-furamide



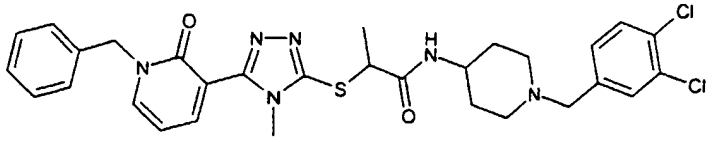
Example 49

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-[3-(4-pyridinyl)-1,2,4-oxadiazol-5-yl]butanamide



Example 50

2-{[5-(1-Benzyl-2-oxo-1,2-dihydro-3-pyridinyl)-4-methyl-4H-1,2,4-triazol-3-yl]sulfanyl}-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]propanamide



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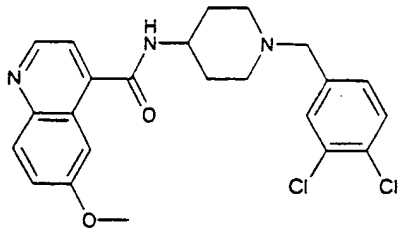
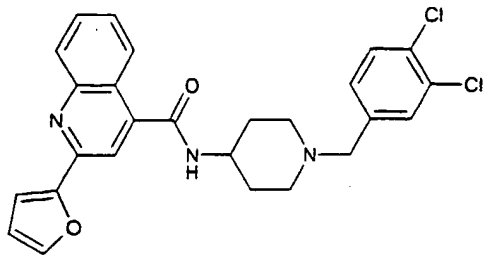
Example 51

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-6-methoxy-4-quinolinecarboxamide



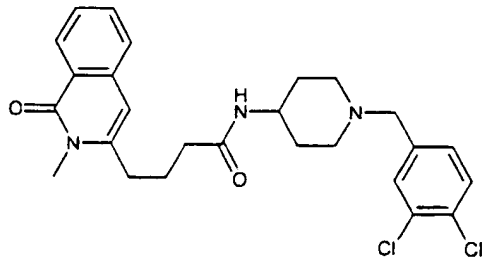
Example 52

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(2-furyl)-4-quinolinecarboxamide



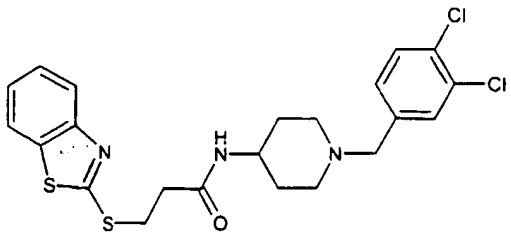
Example 53

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-(2-methyl-1-oxo-1,2-dihydro-3-isoquinolinyl)butanamide



Example 54

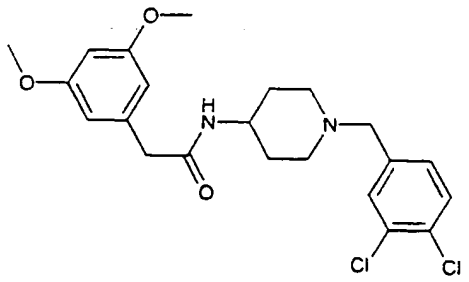
3-(1,3-Benzothiazol-2-ylsulfanyl)-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]propanamide



Example 55

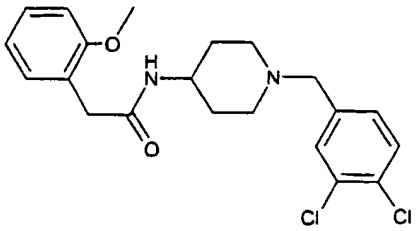
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(3,5-dimethoxyphenyl)acetamide

3NSDOCID: <GB__ 2373186A__I_>



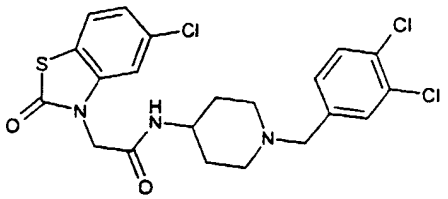
Example 56

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(2-methoxyphenyl)acetamide



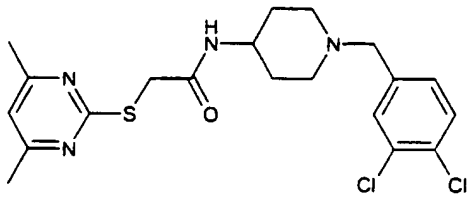
Example 57

2-[5-Chloro-2-oxo-1,3-benzothiazol-3(2H)-yl]-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide



Example 58

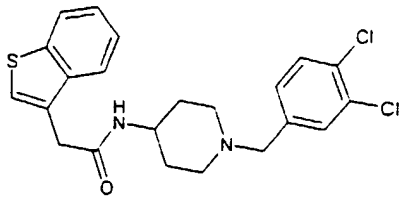
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-[(4,6-dimethyl-2-pyrimidinyl)sulfanyl]acetamide



Example 59

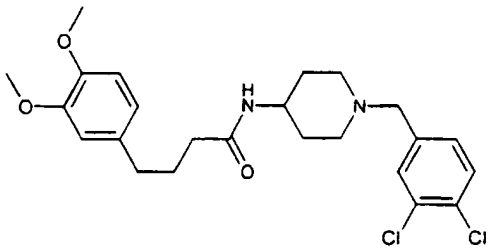
2-(1-Benzothiophen-3-yl)-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide

BNSDOCID: <GB_ _2373186A _I_>



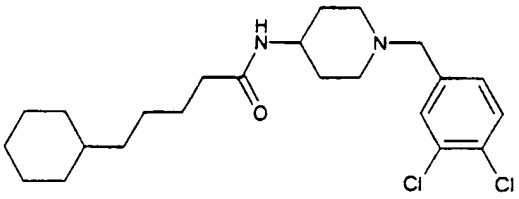
Example 60

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-(3,4-dimethoxyphenyl)butanamide



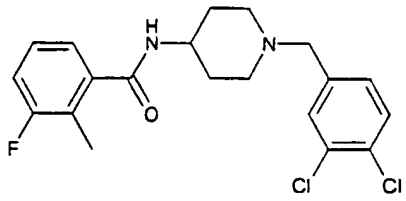
Example 61

5-Cyclohexyl-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]pentanamide



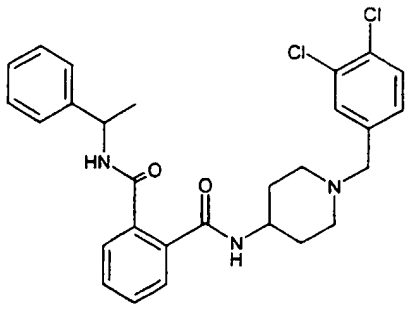
Example 62

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-fluoro-2-methylbenzamide



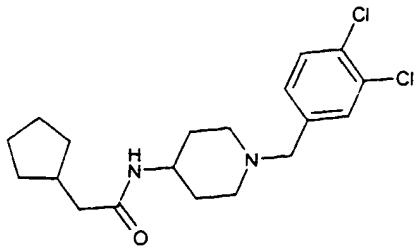
Example 63

N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-(1-phenylethyl)phthalamide



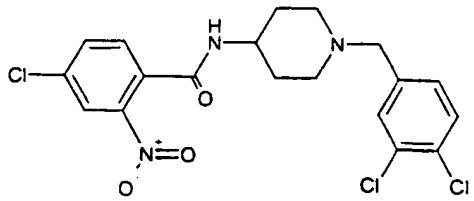
Example 64

2-Cyclopentyl-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide



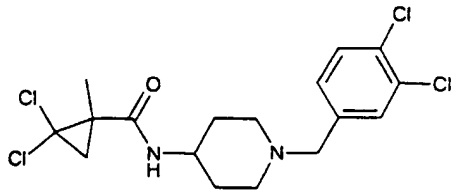
Example 65

4-Chloro-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-nitrobenzamide



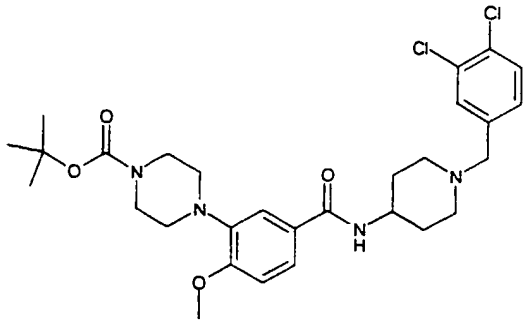
Example 66

2,2-Dichloro-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-1-methylcyclopropanecarboxamide



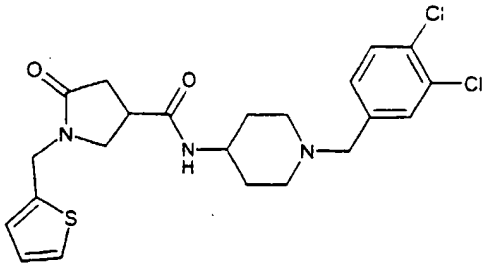
Example 67

tert-Butyl 4-[5-({[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}carbonyl)-2-methoxyphenyl]-1-piperazinecarboxylate



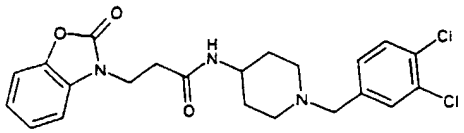
Example 68

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-5-oxo-1-(2-thienylmethyl)-3-pyrrolidinecarboxamide



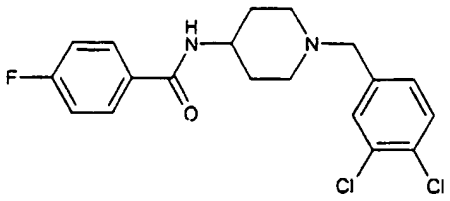
Example 69

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-[2-oxo-1,3-benzoxazol-3(2H)-yl]propanamide



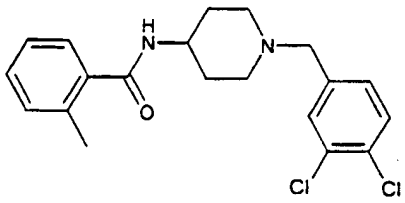
Example 70

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-fluorobenzamide



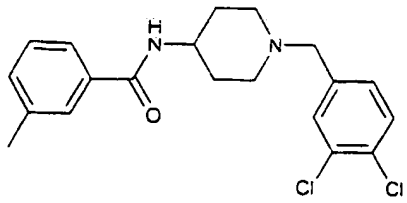
Example 71

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-methylbenzamide



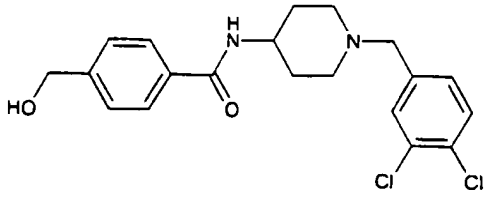
Example 72

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-methylbenzamide



Example 73

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-4-(hydroxymethyl)benzamide

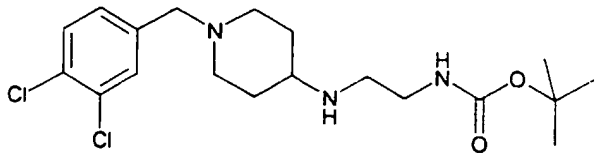


Examples 74-93

Step i: 1-(3,4-Dichlorobenzyl)-4-piperidinone

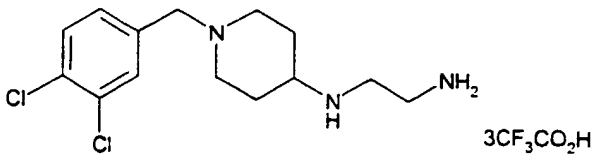
A solution of 3,4-dichlorobenzyl chloride (2.8ml), 4-ketopiperidine hydrochloride monohydrate and triethylamine (8ml) in dimethylformamide (30ml) was stirred at room temperature for 20h. The mixture was partitioned between water and ethyl acetate, the organic layer dried and evaporated under reduced pressure. Purification was by chromatography eluting with 40-50% ethyl acetate/isohexane. Yield 2.1g.

Step ii: tert-Butyl 2-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}ethylcarbamate



A solution of the product from step (i) (1.61g), N-(tert-butoxycarbonyl)-ethylenediamine (1g) and sodium triacetoxyborohydride (2.12g) in dichloromethane (20ml) was stirred at room temperature for 3h. The mixture was partitioned between water and ethyl acetate, the organic layer dried and evaporated under reduced pressure. Yield 1.28g.

Step iii: N-1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-1,2-ethanediamine, tri-trifluoroacetate salt



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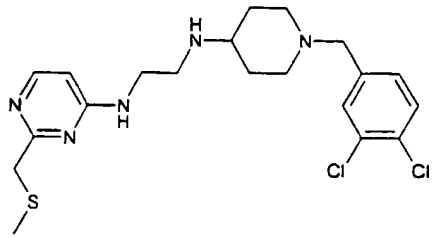
The product from step (ii) (1.28g) was treated with trifluoroacetic acid (5ml) in dichloromethane (10ml). After 20h, the solution was evaporated, the residue triturated with ether and the solid (1.62g) collected.

Step iv: Examples 74-93

The product from step (iii) (0.0026g), the appropriate activated halo-aromatic (1.25 equivalents) and diisopropylethylamine (10 equivalents) in 1-methyl-2-pyrolidinone (0.15ml) was heated at 100°C for 20h. The reaction mixture was evaporated to dryness and the residue dissolved in dimethylsuphoxide (0.4ml).

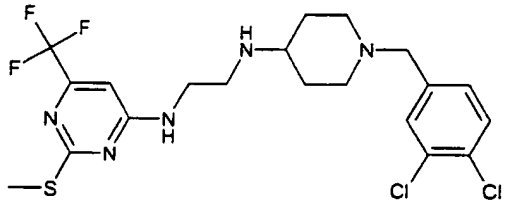
Example 74

N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-{2-[(methylsulfanyl)methyl]-4-pyrimidinyl}-1,2-ethanediamine



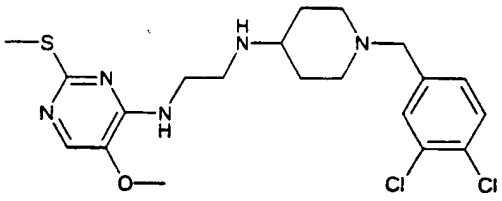
Example 75

N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-[2-(methylsulfanyl)-6-(trifluoromethyl)-4-pyrimidinyl]-1,2-ethanediamine



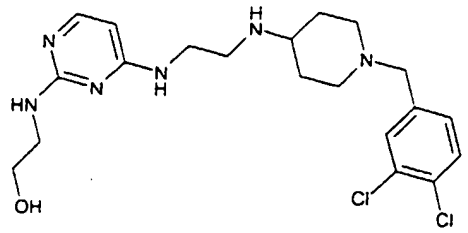
Example 76

N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-[5-methoxy-2-(methylsulfanyl)-4-pyrimidinyl]-1,2-ethanediamine



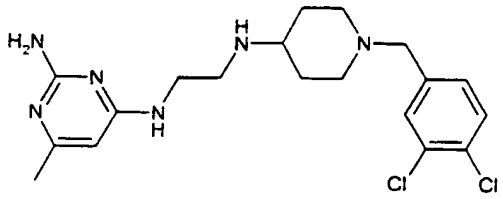
Example 77

2-({4-[(2-{[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}ethyl)amino]-2-pyrimidinyl}amino)-1-ethanol



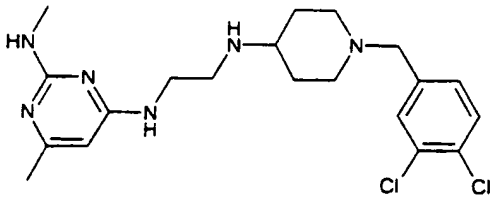
Example 78

N^4-(2-{[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}ethyl)-6-methyl-2,4-pyrimidinediamine



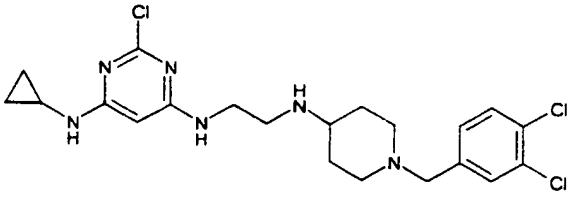
Example 79

N^4-(2-{[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}ethyl)-N^2,6-dimethyl-2,4-pyrimidinediamine



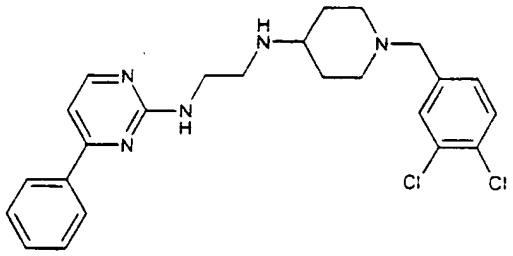
Example 80

2-Chloro-N^4-cyclopropyl-N^6-(2-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}ethyl)-4,6-pyrimidinediamine



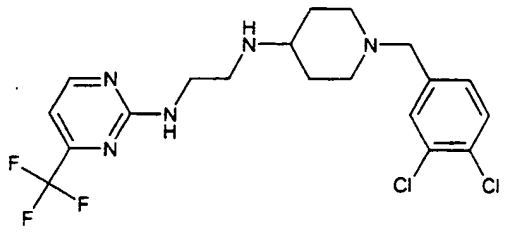
Example 81

N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-(4-phenyl-2-pyrimidinyl)-1,2-ethanediamine



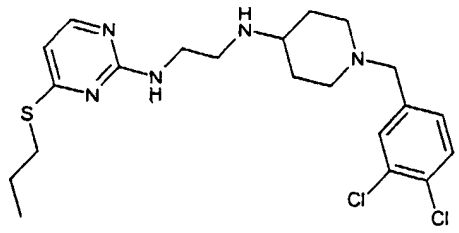
Example 82

N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-[4-(trifluoromethyl)-2-pyrimidinyl]-1,2-ethanediamine



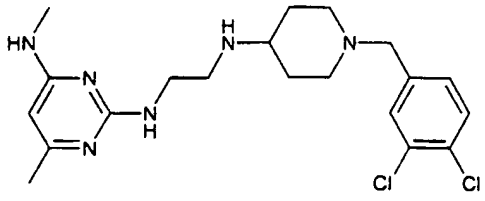
Example 83

N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-[4-(propylsulfanyl)-2-pyrimidinyl]-1,2-ethanediamine



Example 84

N^2-(2-{[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}ethyl)-N^4,6-dimethyl-2,4-pyrimidinediamine



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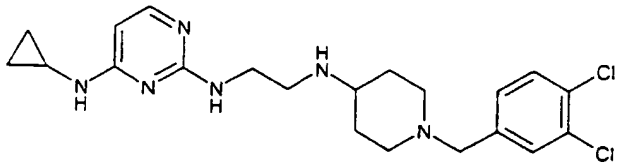
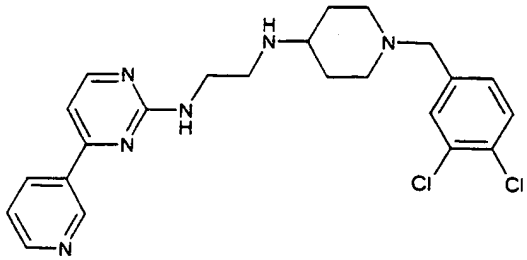
Example 85

N^4-Cyclopropyl-N^2-(2-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}ethyl)-2,4-pyrimidinediamine



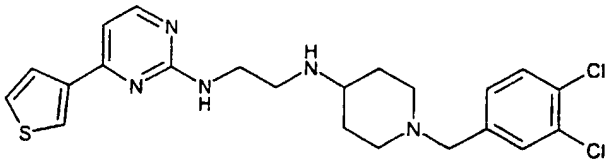
Example 86

N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-[4-(3-pyridinyl)-2-pyrimidinyl]-1,2-ethanediamine



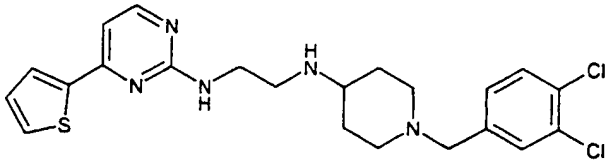
Example 87

N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-[4-(3-thienyl)-2-pyrimidinyl]-1,2-ethanediamine



Example 88

N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-[4-(2-thienyl)-2-pyrimidinyl]-1,2-ethanediamine



Example 89

N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-(1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-1,2-ethanediamine

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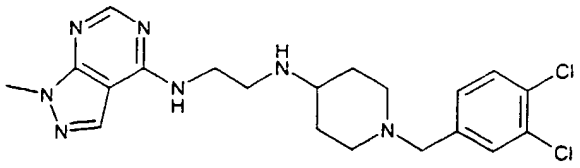
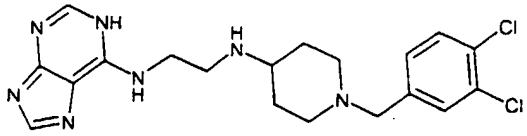


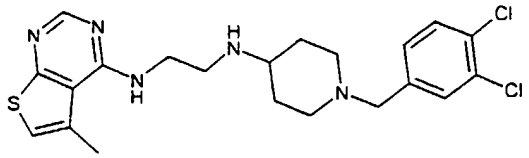
Example 90

N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-(1H-purin-6-yl)-1,2-ethanediamine



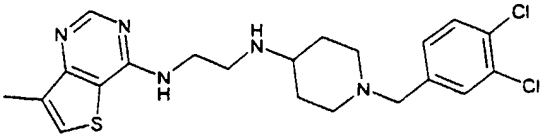
Example 91

N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-(5-methylthieno[2,3-d]pyrimidin-4-yl)-1,2-ethanediamine



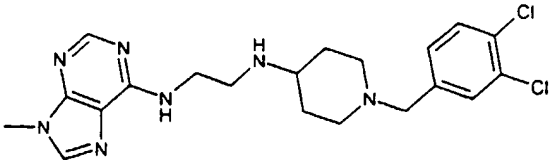
Example 92

N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-(7-methylthieno[3,2-d]pyrimidin-4-yl)-1,2-ethanediamine



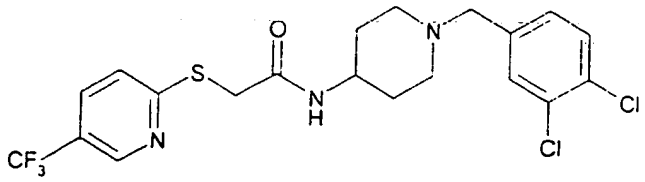
Example 93

N^1-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N^2-(9-methyl-9H-purin-6-yl)-1,2-ethanediamine



Example 94

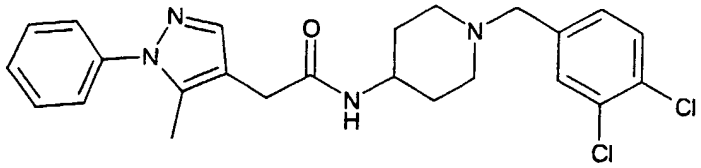
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-{[5-(trifluoromethyl)-2-pyridinyl]sulfanyl}acetamide



Carbonyldiimidazole (0.105g) was added to a stirred solution of 2-{[5-(trifluoromethyl)-2-pyridinyl]sulfanyl}acetic acid (0.166g) in dimethylformamide (2ml). After 1h a solution of the product from 1-(3,4-dichlorobenzyl)-4-piperidinamine, di-trifluoroacetate salt (0.3g) in a solution of dimethylformamide and diisopropylethylamine (2 equivalents) (1.5ml) was added and stirred at room temperature for 2h. The mixture was partitioned between water and ethyl acetate, the organic layer washed with water, dried and evaporated under reduced pressure. The residue was triturated with ether and collected. Yield 0.084g as a solid; MP: 98°C.

Example 95

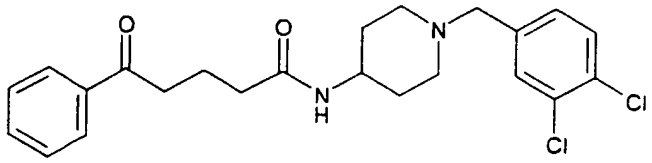
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(5-methyl-1-phenyl-1H-pyrazol-4-yl)acetamide



The title compound was prepared from the product of 1-(3,4-dichlorobenzyl)-4-piperidinamine, di-trifluoroacetate salt (0.3g) and of 2-(5-methyl-1-phenyl-1H-pyrazol-4-yl)acetic acid (0.151g) using the method of Example 94. Yield 0.18g as a solid MP: 165°C.

Example 96

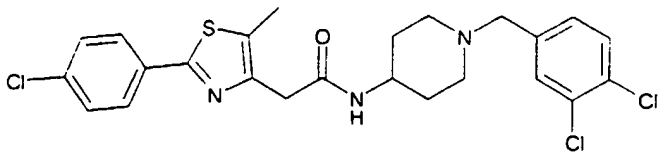
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-5-oxo-5-phenylpentanamide



The title compound was prepared from the product of 1-(3,4-dichlorobenzyl)-4-piperidinamine, di-trifluoroacetate salt (0.3g) and of 5-oxo-5-phenylpentanoic acid (0.134g) using the method of Example 94. Yield 0.149g as a solid MP: 130°C.

Example 97

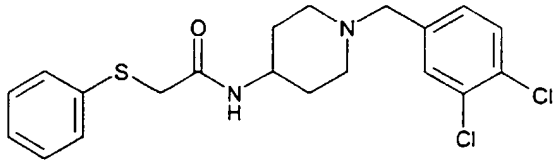
2-[2-(4-Chlorophenyl)-5-methyl-1,3-thiazol-4-yl]-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide



The title compound was prepared from the product of 1-(3,4-dichlorobenzyl)-4-piperidinamine, di-trifluoroacetate salt (0.3g) and 2-[2-(4-chlorophenyl)-5-methyl-1,3-thiazol-4-yl]acetic acid (0.187g) using the method of Example 94. Yield 0.1g as a solid MP: 170°C.

Example 98

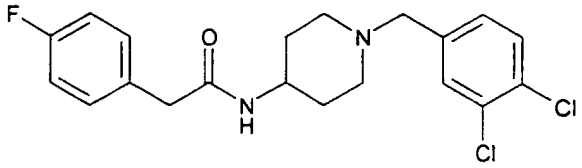
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(phenylsulfanyl)acetamide



The title compound was prepared from the product of 1-(3,4-dichlorobenzyl)-4-piperidinamine, di-trifluoroacetate salt (0.3g) and 2-(phenylsulfanyl)acetic acid (0.118g) using the method of Example 94. Yield 0.056g as a solid MP: 97-99°C.

Example 99

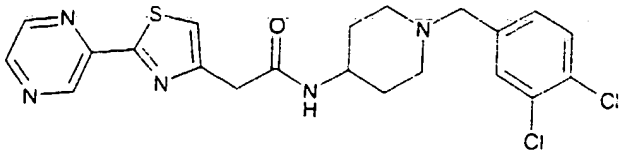
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(4-fluorophenyl)acetamide



The title compound was prepared from the product of 1-(3,4-dichlorobenzyl)-4-piperidinamine, di-trifluoroacetate salt (0.3g) and 2-(4-fluorophenyl)acetic acid (0.108g) using the method of Example 94. Yield 0.15g as a solid MP: 144-7°C.

Example 100

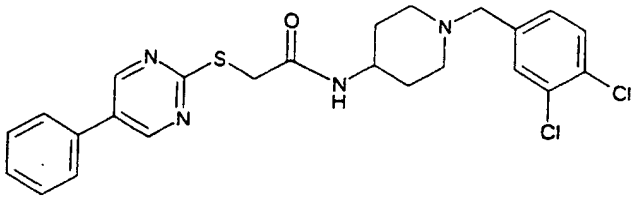
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-[2-(2-pyrazinyl)-1,3-thiazol-4-yl]acetamide



The title compound was prepared from the product of 1-(3,4-dichlorobenzyl)-4-piperidinamine, di-trifluoroacetate salt (0.3g) and 2-[2-(2-pyrazinyl)-1,3-thiazol-4-yl]acetic acid (0.155g) using the method of Example 94. Yield 0.08g as a solid MP: 186-9°C.

Example 101

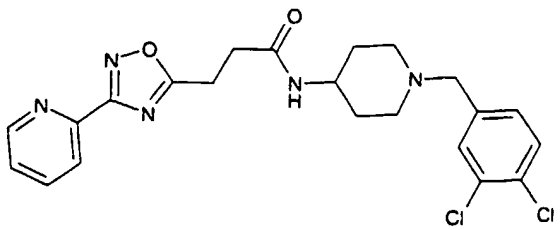
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-[(5-phenyl-2-pyrimidinyl)sulfanyl]acetamide



The title compound was prepared from the product of 1-(3,4-dichlorobenzyl)-4-piperidinamine, di-trifluoroacetate salt (0.3g) and 2-[(5-phenyl-2-pyrimidinyl)sulfanyl]-acetic acid (0.172g) using the method of Example 94. Yield 0.115g as a solid MP: 157°C.

Example 102

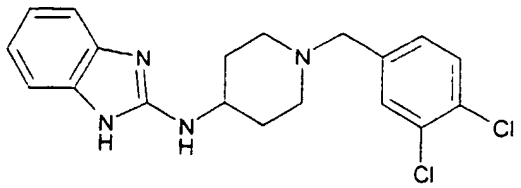
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide



The title compound was prepared from the product of 1-(3,4-dichlorobenzyl)-4-piperidinamine, di-trifluoroacetate salt (0.9g) and 3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanoic acid (0.3g) using the method of Example 94. Yield 0.074g as a solid MP: 155°C.

Example 103

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-1H-benzimidazol-2-amine



(i) Ethyl 4-(1H-benzimidazol-2-ylamino)-1-piperidinecarboxylate

A solution of 2-chlorobenzimidazole (1g) and ethyl 4-amino-1-piperidinecarboxylate (2g) in 1-methyl-2-pyrrolidinone was heated at 130°C for 24h. The mixture was partitioned between water and ethyl acetate, the organic layer washed with water, dried and evaporated under reduced pressure. Purification was by chromatography eluting with 1% triethylamine/5% methanol in dichloromethane. Yield 0.630g as a solid.

(ii) N-(4-Piperidinyl)-1H-benzimidazol-2-amine, dihydrochloride salt

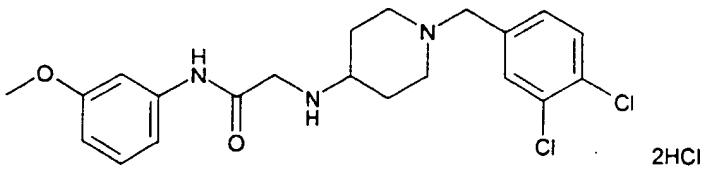
The product from step (i) (0.58g) was heated under reflux with 5M hydrochloric acid (20ml) for 24h. The solvent was evaporated under reduced pressure, the residue azeotroped with toluene, washed with ether. Yield 0.58g as a solid.

(iii) N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-1H-benzimidazol-2-amine

Triethylamine (0.223ml) was added to a stirred suspension of the product from step (ii) (0.2g) in dimethylformamide. After 5min 3,4-dichlorobenzaldehyde (0.175g) then sodium triacetoxyborohydride (0.212g) was added and the mixture stirred at room temperature for 3h. The mixture was partitioned between 2M hydrochloric acid and ether, the aqueous layer was basified with aqueous sodium hydrogencarbonate and extracted with ethyl acetate. The organic layer was dried and evaporated under reduced pressure. The residue was triturated with ethyl acetate/ether and the solid collected. Yield 0.045g MP: 125°C.

Example 104

2-{[1-(3,4-Dichlorobenzyl)-4-piperidinyl]amino}-N-(3-methoxyphenyl)acetamide, dihydrochloride salt

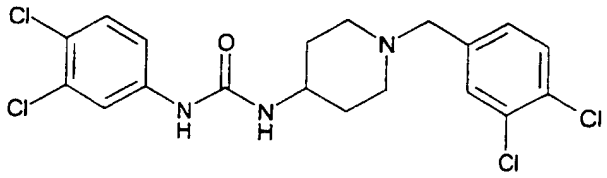


2-Chloro-N-(3-methoxyphenyl)-acetamide (0.241g) was added to a stirred solution of 1-(3,4-dichlorobenzyl)-4-piperidinamine, dihydrochloride salt (0.4g), triethylamine

(0.608g) in 1-methyl-2-pyrrolidinone (5ml). The reaction mixture was heated at 80°C for 6h then partitioned between ethyl acetate and brine. The organic layer was washed with brine, dried and evaporated under reduced pressure. Purification was by chromatography eluting with chloroform/isohexane/triethylamine/methanol 30:15:3:0.5. The resulting product was converted to the hydrochloride salt using ethereal hydrogenchloride. Yield 0.135g MP: 274-6°C.

Example 105

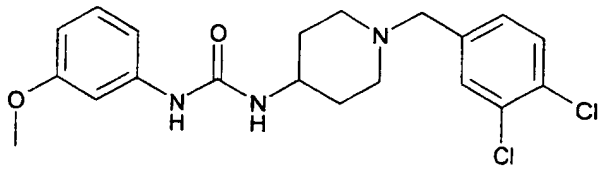
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N'-(3,4-dichlorophenyl)urea



3,4-Dichlorophenyl isocyanate (0.081g) was added to a stirred solution of 1-(3,4-dichlorobenzyl)-4-piperidinamine, di-trifluoroacetate salt (0.13g), diisopropylethylamine (0.2g) in dichloromethane (4ml). The reaction mixture was stirred for 20h and the solvent removed under reduced pressure. Purification was by chromatography eluting with 5% methanol/dichloromethane. Yield 0.09g as a solid MP: 189-190°C.

Example 106

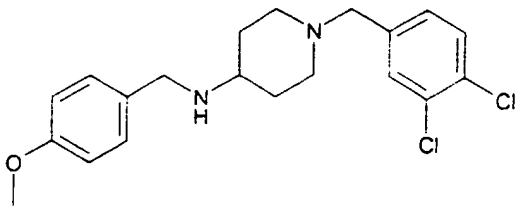
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N'-(3-methoxyphenyl)urea



3-Methoxyphenyl isocyanate (0.064g) was added to a stirred solution of 1-(3,4-dichlorobenzyl)-4-piperidinamine, di-trifluoroacetate salt (0.13g), diisopropylethylamine (0.2g) in dichloromethane (4ml). The reaction mixture was stirred for 20h and the solvent removed under reduced pressure. Purification was by chromatography eluting with 5% methanol/dichloromethane. Yield 0.09g as a solid MP: 178-9°C.

Example 107

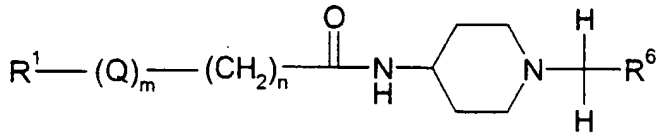
N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-N-(4-methoxybenzyl)amine, dihydrochloride salt



2HCl

The title compound was prepared from 1-(3,4-dichlorobenzyl)-4-piperidinamine, di-trifluoroacetate salt (0.185g) and 4-methoxybenzaldehyde (0.49ul) using the method of Example A step (i). Yield 0.84g as a solid MP: >250°C.

The following table lists Examples 108-348 which are of compounds of formula (I) all of which accord to formula (Ib).



(Ib)

Example	R^1	$(Q)_m$	n	R^6
108	phenyl	m=0	2	3,4-Cl_2-C_6H_3
109	4-Br-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
110	4-NH_2-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
111	2-Br-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
112	4-F-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
113	3-CH_3-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
114	2-CH_3-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
115	3-Cl-4-OH-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
116	2-NO_2-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
117	2-Cl-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
118	4-Cl-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
119	3,4-$(OH)_2$-C_6H_3	m=0	2	3,4-Cl_2-C_6H_3
120	4-NO_2-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
121	phenyl	m=0	4	3,4-Cl_2-C_6H_3
122	3,4-$(OCH_3)_2$-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
123	3-F-4-OH-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
124	3,4-methylenedioxyphenyl	m=0	1	3,4-Cl_2-C_6H_3

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125	4-OH-C_6H_4	m=0	2	3,4-Cl_2-C_6H_3
126	4-OH-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
127	4-phenyl-phenyl	m=0	1	3,4-Cl_2-C_6H_3
128	3,4-Cl_2-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
129	3-OH-C_6H_4	m=0	2	3,4-Cl_2-C_6H_3
130	4-CH_3-C_6H_4	m=0	2	3,4-Cl_2-C_6H_3
131	4-NO_2-C_6H_4	m=0	3	3,4-Cl_2-C_6H_3
132	3,4-$(OCH_3)_2$-C_6H_3	m=0	2	3,4-Cl_2-C_6H_3
133	C_6F_5	m=0	2	3,4-Cl_2-C_6H_3
134	4-CH_3-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
135	4-OCF_3-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
136	3,4-$(OCH_3)_2$-C_6H_3	m=0	3	3,4-Cl_2-C_6H_3
137	4-OCH_3-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
138	4-$N(CH_3)_2$-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
139	4-OCH_3-C_6H_4	m=0	2	3,4-Cl_2-C_6H_3
140	3,4,5-$(OCH_3)_3$-C_6H_2	m=0	1	3,4-Cl_2-C_6H_3
141	3,4-methylenedioxyphenyl	m=0	2	3,4-Cl_2-C_6H_3
142	3-NH_2-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
143	naphth-1-yl	m=0	1	3,4-Cl_2-C_6H_3
144	3-OCH_3-4-OH-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
145	3-(6-Br-1-(prop-2-en-1-yl)-naphth-2-yloxymethyl)phenyl	m=0	1	3,4-Cl_2-C_6H_3
146	4-(4-NO_2-C_6H_4-CH_2O)-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
147	3-F-4-CH_3O-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
148	3-CH_3-C_6H_4	m=0	4	3,4-Cl_2-C_6H_3
149	3-OH-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
150	4-(C_6H_5-CH_2O)-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
151	4-(3-NO_2-C_6H_4)-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
152	2,5-$(CH_3)_2$-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3

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153	4-I-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
154	3-Br-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
155	2-CH_3-3-NO_2-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
156	3-OH-4-OCH_3-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
157	3-F-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
158	2-F-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
159	3,5-$(OCH_3)_2$-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
160	3-Cl-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
161	phenyl	m=0	1	3,4-Cl_2-C_6H_3
162	3,5-$(CH_3)_2$-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
163	3-OCH_3-C_6H_4	m=0	2	3,4-Cl_2-C_6H_3
164	2,4-F_2-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
165	2-OCH_3-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
166	3,4-F_2-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
167	3,5-F_2-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
168	Pyridin-3-yl	m=0	1	3,4-Cl_2-C_6H_3
169	Pyridin-2-yl	m=0	1	3,4-Cl_2-C_6H_3
170	5-Br-pyridin-3-yl	m=0	1	3,4-Cl_2-C_6H_3
171	2,4-$(OCH_3)_2$-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
172	4-(benzyloxy)phenyl	m=0	1	3,4-Cl_2-C_6H_3
173	3-(benzyloxy)phenyl	m=0	1	3,4-Cl_2-C_6H_3
174	2-methyl-naphth-1-yl	m=0	1	3,4-Cl_2-C_6H_3
175	2-CH_3CH_2O-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
176	3,4-$(OCH_3)_2$-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
177	4-$CH_3(CH_2)_3O$-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
178	Indol-1-yl	m=0	1	3,4-Cl_2-C_6H_3
179	2-NO_2-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
180	Thien-2-yl	m=0	1	3,4-Cl_2-C_6H_3
181	3-Cl-4-OH-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
182	2,4-Cl_2-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
183	2,6-Cl_2-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3

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184	2-Br-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
185	3,4-Cl_2-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
186	3-Br-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
187	3,5-F_2-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
188	3-NH_2-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
189	2-($ClCH_2C(O)NH$)-thiazol-4-yl	m=0	1	3,4-Cl_2-C_6H_3
190	3-Cl-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
191	2,5-$(OCH_3)_2$-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
192	4-OH-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
193	Indol-3-yl	m=0	1	3,4-Cl_2-C_6H_3
194	5-OCH_3-indol-3-yl	m=0	1	3,4-Cl_2-C_6H_3
195	Naphth-2-yl	m=0	1	3,4-Cl_2-C_6H_3
196	4-CH_3-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
197	3,4,5-$(OCH_3)_3$-C_6H_2	m=0	1	3,4-Cl_2-C_6H_3
198	4-$CH_3(CH_2)_3O$-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
199	4-$S(O)_2CH_3$-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
200	2,4,6-$(CH_3)_3$-C_6H_2	m=0	1	3,4-Cl_2-C_6H_3
201	4-F-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
202	2-(pyrazin-2-yl)-thiazol-4-yl	m=0	1	3,4-Cl_2-C_6H_3
203	2-CH_3-5-$(CH_3)_2CH$-indol-3-yl	m=0	1	3,4-Cl_2-C_6H_3
204	5-(pyrrolidin-1-yl)-tetrazol-2-yl	m=0	1	3,4-Cl_2-C_6H_3
205	5-(4-CH_3-phenyl)-tetrazol-2-yl	m=0	1	3,4-Cl_2-C_6H_3
206	3,5-F_2-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
207	3-OCH_3-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
208	5-Cl-benzo[b]thiophen-3-yl	m=0	1	3,4-Cl_2-C_6H_3

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209	3,4-Cl_2-C_6H_3	m=0	1	3,4-Cl_2-C_6H_3
210	2-phenyl-5-methyl-thiazol-4-yl	m=0	1	3,4-Cl_2-C_6H_3
211	4-OCF_3-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
212	3-methyl-5-Cl-benzo[b]thiophen-2-yl	m=0	1	3,4-Cl_2-C_6H_3
213	3-methyl-benzo[b]thiophen-2-yl	m=0	1	3,4-Cl_2-C_6H_3
214	2-NO_2-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
215	3-NO_2-1,2,4-triazol-1-yl	m=0	1	3,4-Cl_2-C_6H_3
216	3,4-$(NO_2)_2$-5-CH_3-pyrazol-1-yl	m=0	1	3,4-Cl_2-C_6H_3
217	4-$(CH_3)_2CH(CH_2)_2O$-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
218	2,3-$(CH_3)_2$-indol-5-yl	m=0	1	3,4-Cl_2-C_6H_3
219	3,5-$(CH_3)_2$-4-Cl-pyrazol-1-yl	m=0	1	3,4-Cl_2-C_6H_3
220	3,5-$(CH_3)_2$-4-NO_2-pyrazol-1-yl	m=0	1	3,4-Cl_2-C_6H_3
221	2,4-$(NO_2)_2$-imidazol-1-yl	m=0	1	3,4-Cl_2-C_6H_3
222	4-NO_2-imidazol-1-yl	m=0	1	3,4-Cl_2-C_6H_3
223	3,5-$(CH_3)_2$-pyrazol-1-yl	m=0	1	3,4-Cl_2-C_6H_3
224	4-$CH_3(CH_2)_5$-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
225	2-CN-C_6H_4	m=0	1	3,4-Cl_2-C_6H_3
226	4-Cl-C_6H_4	O	1	4-Cl-C_6H_4
227	4-Cl-C_6H_4	O	1	2-Br-C_6H_4
228	4-Cl-C_6H_4	O	1	3-(CO_2CH_3)-4-Br-C_6H_4
229	4-Cl-C_6H_4	O	1	4-NO_2-C_6H_4
230	4-Cl-C_6H_4	O	1	3-benzoyl-phenyl
231	4-Cl-C_6H_4	O	1	5-OCH_3-benzimidazol-2-yl

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232	4-Cl-C_6H_4	O	1	4-Br-C_6H_4
233	4-Cl-C_6H_4	O	1	4-(1,2,3-thiadiazol-4-yl)-phenyl
234	4-Cl-C_6H_4	O	1	4-CH_3-C_6H_4
235	4-Cl-C_6H_4	O	1	4-(2,6-Cl_2-C_6H_3)$CH_2S(O)_2$-C_6H_4
236	4-Cl-C_6H_4	O	1	3,5-Br_2-C_6H_3
237	4-Cl-C_6H_4	O	1	Indan-5-yl
238	4-Cl-C_6H_4	O	1	2-F-3-Cl-C_6H_3
239	4-Cl-C_6H_4	O	1	benzofurazan-5-yl
240	4-Cl-C_6H_4	O	1	7-Cl-quinolin-2-yl
241	4-F-C_6H_4	m=0	1	2,5-Cl_2-C_6H_3
242	4-F-C_6H_4	m=0	1	2,3-Cl_2-C_6H_3
243	4-F-C_6H_4	m=0	1	4-F-C_6H_4
244	4-F-C_6H_4	m=0	1	3-CO_2CH_3-4-Br-C_6H_3
245	4-F-C_6H_4	m=0	1	4-NO_2-C_6H_4
246	4-F-C_6H_4	m=0	1	3-benzoyl-phenyl
247	4-F-C_6H_4	m=0	1	4-CH_3-naphth-1-yl
248	4-F-C_6H_4	m=0	1	3,4-methylene-dioxyphenyl
249	4-F-C_6H_4	m=0	1	5-OCH_3-benzimidazol-2-yl
250	4-F-C_6H_4	m=0	1	3-NO_2-4-CH_3-C_6H_3
251	4-F-C_6H_4	m=0	1	3,4-$(CH_3)_2$-C_6H_3
252	4-F-C_6H_4	m=0	1	3-CH_3-4-OCH_3-C_6H_3
253	4-F-C_6H_4	m=0	1	4-(2-$C(O)NH_2$-C_6H_4)-C_6H_4

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254	4-F-C_6H_4	m=0	1	4-Br-C_6H_4
255	4-F-C_6H_4	m=0	1	4-(2,6-Cl_2-C_6H_4)$CH_2S(O)_2$-C_6H_4
256	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	4-Cl-C_6H_4
257	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	3-Cl-4-OCH_3-C_6H_3
258	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	2,3-Cl_2-C_6H_3
259	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	4-F-C_6H_4
260	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	3-CF_3-C_6H_4
261	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	4-NO_2-C_6H_4
262	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	3-benzoyl-phenyl
263	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	3,4-methylene-dioxyphenyl
264	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	3,5-$(CH_3)_2$-C_6H_3
265	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	3-NO_2-4-CH_3-C_6H_3
266	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	3,4-$(CH_3)_2$-C_6H_3
267	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	3-CH_3-C_6H_4
268	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	3-CH_3-4-OCH_3-C_6H_4

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269	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	4-Br-C_6H_4
270	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	Indan-5-yl
271	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	4-CF_3-C_6H_4
272	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	Naphth-2-yl
273	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	4-CH_3-C_6H_4
274	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	benzofurazan-5-yl
275	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	3,4-F_2-C_6H_3
276	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	7-Cl-quinolin-2-yl
277	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	3-Cl-C_6H_4
278	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	4-CF_3-C_6H_4
279	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	m=0	2	4-CH_3-C_6H_4
280	4-OCH_3-C_6H_4	O	1	3,4-Cl_2-C_6H_3
281	4-Cl-C_6H_4	O	1	3,4-Cl_2-C_6H_3
282	4-NO_2-C_6H_4	O	1	3,4-Cl_2-C_6H_3
283	4-$NHC(O)CH_3$-C_6H_4	O	1	3,4-Cl_2-C_6H_3
284	4-$O(CH_2)_2CH_3$-C_6H_4	O	1	3,4-Cl_2-C_6H_3
285	3-$CO_2CH_2CH_3$-C_6H_4	O	1	3,4-Cl_2-C_6H_3
286	2-$C(CH_3)_3$-C_6H_4	O	1	3,4-Cl_2-C_6H_3
287	2-$NHC(O)CH_3$-C_6H_4	O	1	3,4-Cl_2-C_6H_3

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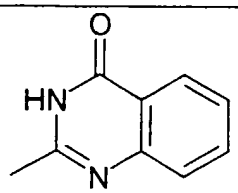
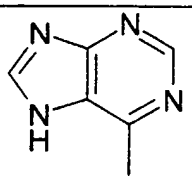
288	3,5-$(OCH_3)_2$-C_6H_3	O	1	3,4-Cl_2-C_6H_3
289	2-OCH_3-5-NO_2-C_6H_3	O	1	3,4-Cl_2-C_6H_3
290	4-CN-C_6H_4	O	1	3,4-Cl_2-C_6H_3
291	2-Cl-5-CF_3-C_6H_3	O	1	3,4-Cl_2-C_6H_3
292	2-NO_2-5-CH_3-C_6H_3	O	1	3,4-Cl_2-C_6H_3
293	3-Cl-5-OCH_3-C_6H_3	O	1	3,4-Cl_2-C_6H_3
294	3-NO_2-C_6H_4	O	1	3,4-Cl_2-C_6H_3
295	3-Br-C_6H_4	O	1	3,4-Cl_2-C_6H_3
296	4-I-C_6H_4	O	1	3,4-Cl_2-C_6H_3
297	3,5-F_2-C_6H_3	O	1	3,4-Cl_2-C_6H_3
298	4,6-$(NH_2)_2$-pyrimidin-2-yl	S	1	3,4-F_2-C_6H_3
299	Benzimidazol-2-yl	S	1	3,4-F_2-C_6H_3
300	Thiazol-2-yl	S	1	3,4-F_2-C_6H_3
301		S	1	3,4-F_2-C_6H_3
302	5-NO_2-benzimidazol-2-yl	S	1	3,4-F_2-C_6H_3
303	Pyridin-2-yl	S	1	3,4-F_2-C_6H_3
304		S	1	3,4-F_2-C_6H_3
305	1H-1,2,4-triazol-3-yl	S	1	3,4-F_2-C_6H_3
306	Pyrimidin-2-yl	S	1	3,4-F_2-C_6H_3
307	1-phenyl-tetrazol-5-yl	S	1	3,4-F_2-C_6H_3
308	4,6-$(CH_3)_2$-pyrimidin-2-yl	S	1	3,4-F_2-C_6H_3
309	4-(thiophen-2-yl)-pyrimidin-2-yl	S	1	3,4-F_2-C_6H_3
310	2-(cyclopropyl-CH_2S)-1,3,4-thiadiazol-5-yl	S	1	3,4-F_2-C_6H_3

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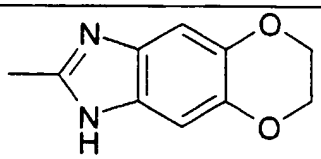
311	4-methyl-3-(thiophen-2-yl)-1,2,4-triazol-5-yl	S	1	3,4-F_2-C_6H_3
312	3-CN-6-($CH_3C(O)$)-pyridin-2-yl	S	1	3,4-F_2-C_6H_3
313	1H-pyrazolo[3,4-d]pyrimidin-4-yl	S	1	3,4-F_2-C_6H_3
314	5-OCH_3-benzimidazol-2-yl	S	1	3,4-F_2-C_6H_3
315	5-F-6-Cl-benzimidazol-2-yl	S	1	3,4-F_2-C_6H_3
316	4,5-dihydrothiazol-2-yl	S	1	3,4-F_2-C_6H_3
317	1H-5-phenyl-1,2,4-triazol-3-yl	S	1	3,4-F_2-C_6H_3
318	2-(thiophen-2-yl)-1,3,4-oxadiazol-5-yl	S	1	3,4-F_2-C_6H_3
319	Quinoxalin-2-yl	S	1	3,4-F_2-C_6H_3
320	2,5-Cl_2-C_6H_3	S	1	3,4-F_2-C_6H_3
321	2-(pyridin-2-yl)-1,3,4-oxadiazol-5-yl	S	1	3,4-F_2-C_6H_3
322	7-CF_3-quinolin-4-yl	S	1	3,4-F_2-C_6H_3
323	2-(pyridin-2-yl)-4-CH_3-pyrimidin-6-yl	S	1	3,4-F_2-C_6H_3
324	Naphth-1-yl	S	1	3,4-F_2-C_6H_3
325	3,4-$(OCH_3)_2$-C_6H_3	S	1	3,4-F_2-C_6H_3
326	1,3,4-thiadiazol-2-yl	S	1	3,4-F_2-C_6H_3
327	3-CF_3-C_6H_4	S	1	3,4-F_2-C_6H_3
328		S	1	3,4-F_2-C_6H_3
329	3,4-Cl_2-C_6H_3	S	1	3,4-F_2-C_6H_3
330	3-CN-5-CH_3-pyridin-2-yl	S	1	3,4-F_2-C_6H_3

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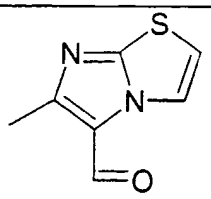
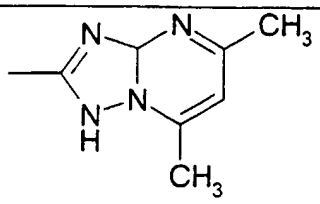
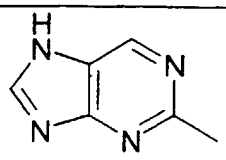
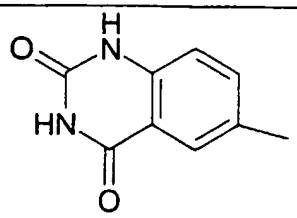
331	4-phenyl-thiazol-2-yl	S	1	3,4-F_2-C_6H_3
332		S	1	3,4-F_2-C_6H_3
333	2-CH_3-1,3,4-thiadiazol-5-yl	S	1	3,4-F_2-C_6H_3
334		S	1	3,4-F_2-C_6H_3
335		S	1	3,4-F_2-C_6H_3
336	2-phenoxy-phenyl	S	1	3,4-F_2-C_6H_3
337	2-OCH_3-C_6H_4	S	1	3,4-F_2-C_6H_3
338	2-CH_3-4-Cl-C_6H_3	S	1	3,4-F_2-C_6H_3
339	2-CH_3-6-Cl-C_6H_3	S	1	3,4-F_2-C_6H_3
340	2-($HC\equiv C$-CH_2S)-1,3,4-thiadiazol-5-yl	S	1	3,4-F_2-C_6H_3
341	2-CO_2CH_3-C_6H_4	S	1	3,4-F_2-C_6H_3
342	4-CN-C_6H_4	O	1	3,4-F_2-C_6H_3
343	4-($(CH_3)_2NCH_2$)-C_6H_4	O	1	3,4-F_2-C_6H_3
344		O	1	3,4-F_2-C_6H_3
345	3-CH_2OH-C_6H_4	O	1	3,4-F_2-C_6H_3
346	2-OCH_2CH_2OH-C_6H_4	O	1	3,4-F_2-C_6H_3
347	4-$CH_3(CH_2)_2O$-C_6H_4	O	1	3,4-F_2-C_6H_3

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348	3-Cl-5-OCH_3-C_6H_3	O	1	3,4-F_2-C_6H_3

General Preparation of Examples 108-225

PyBroP® (bromo-tris-pyrrolidino-phosphonium hexafluorophosphate, 2 equivalents) was added to a solution of 1-(3,4-dichlorobenzyl)-4-piperidinamine, hydrochloride salt (1mg) the appropriate acid (2 equivalents) and triethylamine in 1-methyl-2-pyrrolidone (0.2ml) and was left for 24h. The reaction mixture was evaporated to dryness and the residue was dissolved in dimethylsulfoxide (0.3ml).

General Preparation of Examples 225-240

Step i: *tert*-Butyl 4-{[(4-chlorophenoxy)acetyl]amino}-1-piperidinecarboxylate

Prepared following the method of Example 94 using (4-chlorophenoxy)acetic acid (0.50g), 1,1-carbonyldiimidazole (0.50g) and *tert*-butyl 4-amino-1-piperidinecarboxylate (0.46g) to give the subtitle compound (0.54g).

Step ii: 2-(4-chlorophenoxy)-*N*-(4-piperidinyl)acetamide

Prepared following the method of Example A step (ii) using *tert*-butyl 4-{[(4-chlorophenoxy)acetyl]amino}-1-piperidinecarboxylate (0.52g) to give the subtitle compound (0.35g).

Step iii: Final product

A mixture of the product from step (ii) (1.07mg), the appropriate alkyl halide (2 equivalents) and *N,N*-diisopropylethylamine (3 equivalents) in 1-methyl-2-pyrrolidinone (0.18ml) was left at room temperature for 24h. The mixture was evaporated to dryness and the residue was dissolved in dimethylsulfoxide (0.4ml).

General Preparation of Examples 241-255

A mixture of 2-(4-fluorophenyl)-*N*-(4-piperidinyl)acetamide (WO97/36871; 0.94mg), the appropriate alkyl halide (2 equivalents) and *N,N*-diisopropylethylamine (3 equivalents) in 1-methyl-2-pyrrolidinone (0.18ml) was left at room temperature for 24h. The mixture was evaporated to dryness and the residue was dissolved in dimethylsulfoxide (0.4ml).

General Preparation of Examples 256-279

Step i: *tert*-Butyl 4-({3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanoyl}amino)-1-piperidinecarboxylate

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3-[3-(2-Pyridinyl)-1,2,4-oxadiazol-5-yl]propanoic acid (0.60g) was dissolved in dichloromethane (10ml). 1,1-Carbonyldiimidazole (0.33g) was added followed by *tert*-butyl 4-amino-1-piperidinecarboxylate hydrochloride (0.5g) and triethylamine (0.31ml). After 2hours water, brine and dichloromethane were added and the phases separated. The organic phase was dried, filtered and evaporated and the residue was purified by chromatography eluting with ethyl acetate : methanol (33:1) to give the subtitle compound (0.40g).

Step ii: *N*-(4-Piperidinyl)-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide

tert-Butyl 4-({3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanoyl}amino)-1-piperidinecarboxylate (0.40g) was dissolved in dichloromethane (6ml) and trifluoroacetic acid (3ml) was added. After 2hours water, 2N sodium hydroxide and dichloromethane were added and the phases were separated. The organic phase was dried, filtered and evaporated to give the subtitle compound (0.19g).

Step iii: Final product

A mixture of the product from step (ii) (1.21mg), the appropriate alkyl halide (2 equivalents) and *N,N*-diisopropylethylamine (3 equivalents) in 1-methyl-2-pyrrolidinone (0.18ml) was left at room temperature for 24h. The mixture was evaporated to dryness and the residue was dissolved in dimethylsulfoxide (0.4ml).

General Preparation of Examples 280-296

Step i: 2-Chloro-*N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide

Prepared following the general preparation method of Examples 297-357 step (iii) using 1-(3,4-dichlorobenzyl)-4-piperidinamine hydrochloride (2.0g), *N,N*-diisopropylethylamine (5.55 ml) and chloroacetyl chloride (0.55ml) to give the subtitle compound (1.0g).

Step ii: Final Product

A mixture of the product from step (i) (1.34 mg), the appropriate phenol (1.5 equivalents) and potassium *tert*-butoxide (1.4 equivalents) in 1-methyl-2-pyrrolidinone (0.13ml) was left at room temperature for 24hours. The mixture was evaporated to dryness and the residue was dissolved in dimethylsulfoxide (0.4ml).

General Preparation of Examples 297-340

Step i: Carbamic acid, [1-[(3,4-difluorophenyl)methyl]-4-piperidinyl]-, 1,1-dimethylethyl ester

Carbamic acid, 4-piperidinyl-, 1,1-dimethylethyl ester (6.95g) was dissolved in *N*,*N*-dimethylformamide (70ml). 3,4-Difluorobenzylbromide (4.55ml) and potassium carbonate (16.0g) were added. The mixture was heated to reflux for 16hours, then allowed to cool to room temperature. Ammonium chloride solution was added and the mixture was extracted thrice with ethyl acetate. The organic phases were washed with water (twice) and brine, then dried, filtered and evaporated. The residue was triturated with ether : *iso*-hexane (1:1) to give the subtitle compound (8.13g)

Step ii: 1-[(3,4-Difluorophenyl)methyl]-piperidin-4-ylamine dihydrochloride

Carbamic acid, [1-[(3,4-difluorophenyl)methyl]-4-piperidinyl]-, 1,1-dimethylethyl ester was suspended in 6N hydrochloric acid (100ml). After 16hours excess hydrochloric acid was evaporated and the residue azeotroped with toluene, dried and evaporated to give the subtitle compound (8.10g).

Step iii: 2-Chloro-*N*-[1-[(3,4-difluorophenyl)methyl]-piperidin-4-yl]-acetamide

1-[(3,4-Difluorophenyl)methyl]-piperidin-4-ylamine dihydrochloride (3.18g) was dissolved in tetrahydrofuran (40ml). Diisopropylethylamine (6.84g) and chloroacetyl chloride (1.33g) were added. After 3hours water, brine and ethyl acetate were added the phase were separated. The organic phase was dried, filtered and evaporated and the residue was purified by chromatography eluting with ethyl acetate to give the subtitle compound (0.728g).

Step iv: Final Product

The product from step (iii) (1.21mg) was dissolved in dimethylsulfoxide (50µl) and diisopropylethylamine (1.55mg, 3 equivalents) was added as a solution in dimethylsulfoxide (50µl). The appropriate thiol was added (1 equivalent) in dimethylsulfoxide (40µl) and the reaction mixture was left at room temperature for 24hours. The reaction mixture was evaporated to dryness and the residue was dissolved in dimethylsulfoxide (400µl).

General Preparation of Examples 341-348

Prepared from the product of general preparation for Examples 297-340 step (iii) and the appropriate phenol following the method of Examples 280-296 step (ii).

Example 351

3-[3-(4-Bromo-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-5-yl]-*N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]propanamide

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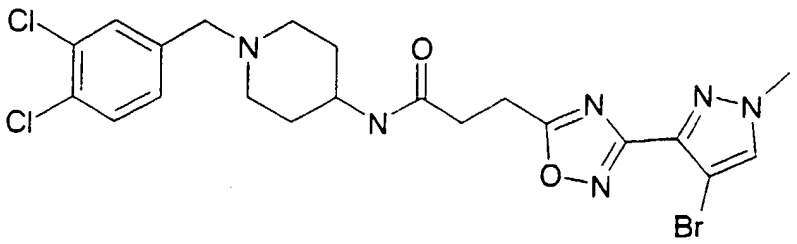

Step i: Methyl 4-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-4-oxobutanoate

To a solution of 1-(3,4-dichlorobenzyl)-4-piperidinamine hydrochloride (3.50g) in dichloromethane (100ml) was added methyl 4-chloro-4-oxobutanoate (2.00g) dropwise. Triethylamine (3.90g) was added and the reaction stirred under nitrogen for 2 hours. Saturated sodium hydrogen carbonate solution was then added, with the solution being extracted three times with dichloromethane. The pooled organic phase was washed once with water, once with saturated brine and dried over anhydrous magnesium sulfate. After filtration the solvent was removed under reduced pressure to leave methyl 4-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-4-oxobutanoate (3.00g).

Step ii: Lithium 4-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-4-oxobutanoate

To a solution of methyl 4-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-4-oxobutanoate (3.72g) in methanol (30ml) was added lithium hydroxide (0.41g) in water (10ml) which was stirred under nitrogen for 48 hours. The solvent was removed under reduced pressure, the residue was triturated with ether and filtered to leave lithium 4-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-4-oxobutanoate (3.50g).

Step iii: 3-[3-(4-Bromo-1-methyl-1*H*-pyrazol-3-yl)-1,2,4-oxadiazol-5-yl]-*N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]propanamide

To lithium 4-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-4-oxobutanoate (0.292g) in dichloromethane (6ml) was added dimethylformamide (1.5ml), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.183g), 1-hydroxybenzotriazole hydrate (0.130g), 4-bromo-*N*'-hydroxy-1-methyl-1*H*-pyrazole-3-carboximidamide (0.175g) and triethylamine (0.161g). Reaction was left to stir for 24 hours before removal of dichloromethane under reduced pressure. Pyridine (5ml) was added and heated at reflux for 5 hours. Pyridine was removed under reduced pressure, followed by the addition of water. The solution was extracted three times with dichloromethane. The pooled organic phase was washed once with water, once with saturated brine and dried over magnesium sulfate. After filtration the product was

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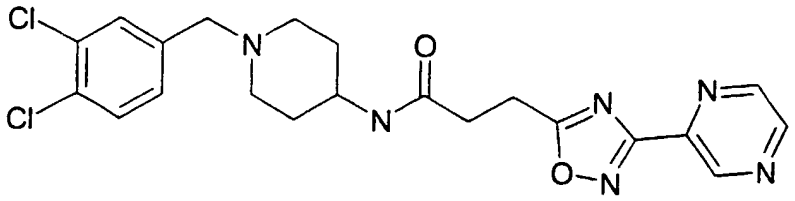
azeotroped twice with toluene and was purified by reverse phase hplc (RPHPLC; 75%-5%, 0.1% ammonium acetate/ acetonitrile). Solvent was removed under reduced pressure to give the titled compound (0.164g).

Example 352

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-[3-(2-pyrazinyl)-1,2,4-oxadiazol-5-yl]propanamide



To lithium 4-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}-4-oxobutanoate (Example 351, step ii) (0.292g) in dichloromethane (6ml) was added *N*,*N*-dimethylformamide (1.5ml), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.183g), 1-hydroxybenzotriazole hydrate (0.130g), *N'*-hydroxy-2-pyrazinecarboximidamide (0.110g) and triethylamine (0.161g). The reaction mixture was left to stir for 24 hours before removal of dichloromethane under reduced pressure. Pyridine (5ml) was added and heated at reflux for 5 hours. Pyridine was removed under reduced pressure followed by the addition of water. The solution was extracted three times with dichloromethane. The pooled organic phase was washed once with water, once with saturated brine and dried over magnesium sulfate. After filtration the product was azeotroped twice with toluene and was purified by RPHPLC (75%-5%, 0.1% ammonium acetate/ acetonitrile). Solvent was removed under reduced pressure to give the title compound (0.067g).

Example 353

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-{3-[(2-thienylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl}propanamide hydrochloride

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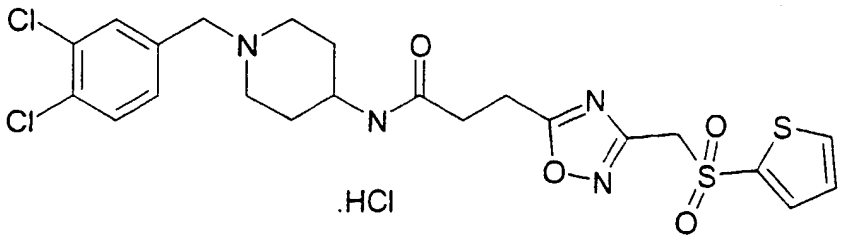

Step i: 3-{3-[(2-Thienylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl}propanoic acid

(1*Z*)-*N'*-hydroxy-2-(2-thienylsulfonyl)ethanimidamide (0.250g) with dihydro-2,5-furandione (0.114g) in dimethylformamide (0.2ml) was heated at 120°C for 2 hours. The reaction was allowed to cool and triturated with diethyl ether and filtered to leave 3-{3-[(2-thienylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl}propanoic acid (0.332g).

Step ii: *N*-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-{3-[(2-thienylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl}propanamide hydrochloride

3-{3-[(2-Thienylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl}propanoic acid (0.332g) in dichloromethane was stirred under nitrogen. Oxalyl chloride (0.252g) was added dropwise followed by the addition of one drop of dimethylformamide. After 30 minutes the solvent and oxalyl chloride was removed under reduced pressure followed by the addition of dichloromethane (10ml), 1-(3,4-dichlorobenzyl)-4-piperidinamine hydrochloride (0.347g), and triethylamine (0.202g) and allowed to stir for 2 hours under nitrogen. Saturated sodium hydrogen carbonate was added to the reaction with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to leave a brown oil. This oil was purified by RPHPLC (75%-5%, 0.1% ammonium acetate/ acetonitrile) followed by chromatography using 3% ethanol/ dichloromethane. The solvent was removed under reduced pressure, followed by the addition of hydrogen chloride in diethyl ether, filtered and dried to leave *N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-3-{3-[(2-thienylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl}propanamide hydrochloride (0.04g) as a pale yellow solid.

Example 354

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-[3-(4-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide

Step i: 3-[3-(4-Pyridinyl)-1,2,4-oxadiazol-5-yl]propanoic acid

N'-hydroxy-4-pyridinecarboximidamide (0.300g) with dihydro-2,5-furandione (0.217g) in dimethylformamide (2 drops) was heated for 4 times 30 seconds in a CEM MARS 5 microwave at 100% of 300W to leave a fused mass. The reaction was allowed to cool and triturated with ethanol and filtered to leave 3-[3-(4-pyridinyl)-1,2,4-oxadiazol-5-yl]propanoic acid (0.241g).

Step ii: *N*-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-[3-(4-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide

For method refer to Example 353 step ii. Purification was performed via chromatography (2.5% ethanol/ dichloromethane). Solvent removed under reduced pressure to leave *N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-3-[3-(4-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide (0.154g) as a pale cream solid.

Example 355

Cis-*N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]cyclopropanecarboxamide

Step i: Cis-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]cyclopropanecarboxylic acid

N'-hydroxy-2-pyridinecarboximidamide (0.137g) with 3-oxabicyclo[3.1.0]hexane-2,4-dione (0.112g) in dimethylformamide (2 drops) was heated for 4 times 30 seconds in a CEM MARS 5 microwave at 100% of 300W to leave a fused mass. The reaction was allowed to cool and triturated with diethyl ether and filtered to leave cis-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]cyclopropanecarboxylic acid (0.200g).

Step ii: Cis-*N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]cyclopropanecarboxamide

Cis-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]cyclopropanecarboxylic acid (0.139g) and N,N'-carbonyldiimidazole (0.110g)in dichloromethane was stirred under nitrogen for 1 hour. 1-(3,4-dichlorobenzyl)-4-piperidinamine hydrochloride (0.198g), and triethylamine (0.121g) was then added and allowed to stir for 24 hours under nitrogen. Saturated sodium hydrogen carbonate was added to the reaction with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to leave an oil. This oil was purified by RPHPLC (75%-5%, 0.1% ammonium acetate/ acetonitrile). The solvent was removed under reduced pressure to

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leave Cis-*N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]cyclopropanecarboxamide (0.054g) as a white solid.

Example 356

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1*H*-1,2,4-triazol-5-yl]propanamide

Step i: 3-[3-(2-Pyridinyl)-1*H*-1,2,4-triazol-5-yl]propanoic acid

2-Pyridinecarbohydrazonamide (0.136g) and dihydro-2,5-furandione (0.100g) in 1 ml of dimethylacetamide was heated for 10 times 30 seconds in a CEM MARS 5 microwave at 100% of 300W under nitrogen to leave 3-[3-(2-pyridinyl)-1*H*-1,2,4-triazol-5-yl]propanoic acid in 1ml of dimethylacetamide.

Step ii: *N*-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1*H*-1,2,4-triazol-5-yl]propanamide

3-[3-(2-Pyridinyl)-1*H*-1,2,4-triazol-5-yl]propanoic acid (0.218g in 1ml dimethylacetamide) and N,N'-carbonyldiimidazole (0.250g) in dichloromethane was stirred under nitrogen for 30 minutes. 1-(3,4-Dichlorobenzyl)-4-piperidinamine hydrochloride (0.316g), and triethylamine (0.218g) was then added and allowed to stir for 2 hours under nitrogen. 1M sodium hydroxide was added to the reaction with the resulting solution being washed three times with dichloromethane. The aqueous phase was acidified with glacial acetic acid, with the water/ acetic acid being removed under reduced pressure. Water was then added and extracted three times with dichloromethane. The pooled organic phases were extracted once with water and the water removed under reduced pressure to leave a white solid. This was then triturated with diethyl ether/ dichloromethane, filtered and was purified by RPHPLC (75%-5%, 0.1% ammonium acetate/ acetonitrile), solvent removed to leave *N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1*H*-1,2,4-triazol-5-yl]propanamide (0.02g).

Example 357

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(3-phenyl-1*H*-1,2,4-triazol-5-yl)acetamide

(3-Phenyl-1*H*-1,2,4-triazol-5-yl)acetic acid (0.020g) and N,N'-carbonyl diimidazole (0.016g) in dichloromethane was stirred under nitrogen for 30 minutes. 1-(3,4-Dichlorobenzyl)-4-piperidinamine hydrochloride (0.031g) and triethylamine (0.036g) was then added and allowed to stir for 1 hour under nitrogen. Saturated sodium hydrogen carbonate was added to the reaction with the resulting solution being extracted three times

with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to a white solid. This was purified by RPHPLC (75%-5%, 0.1% ammonium acetate/ acetonitrile). Saturated sodium hydrogen carbonate was added to the pooled collected fractions with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to leave *N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-(3-phenyl-1*H*-1,2,4-triazol-5-yl)acetamide(0.031g).

Example 358

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-(5-phenyl-1,3,4-oxadiazol-2-yl)acetamide acetate

3-(5-Phenyl-1,3,4-oxadiazol-2-yl)propanoic acid (0.175g) and N,N'-carbonyldiimidazole (0.148g) in dichloromethane was stirred under nitrogen for 30 minutes. 1-(3,4-Dichlorobenzyl)-4-piperidinamine hydrochloride (0.263g), and triethylamine (0.126g) was then added and allowed to stir for 2 hours under nitrogen. Saturated sodium hydrogen carbonate was added to the reaction, with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to leave a cream solid. This solid was purified by chromatography using 2.5% ethanol/ dichloromethane. The solvent was removed under reduced pressure and was purified by RPHPLC (75%-5%, 0.1% ammonium acetate/ acetonitrile), followed by 1 ml of glacial acetic acid being added and the solvent removed under reduced pressure to leave *N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-(5-phenyl-1,3,4-oxadiazol-2-yl)acetamide acetate (0.024g).

Example 359

N-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]acetamide

Step i: Lithium [3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]acetate

2-(5-Methyl-1,2,4-oxadiazol-3-yl)pyridine (0.150g) was stirred at -78°C in dry tetrahydrofuran under nitrogen. (1.6M) *n*-butyl lithium (0.757ml) was added dropwise so as to maintain the temperature at -78°C. After 30 minutes carbon dioxide was passed

through the solution and the reaction was allowed to return to room temperature. Once the reaction had reached room temperature, water (1ml) was added and all solvents were removed under reduced pressure to leave a yellow solid. This solid was triturated with ethyl acetate and filtered to leave a pale yellow solid (0.150g).

Step ii: *N*-[1-(3,4-Dichlorobenzyl)-4-piperidinyl]-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]acetamide

Lithium [3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]acetate (0.140g), 1-(3,4-dichlorobenzyl)-4-piperidinamine (0.170g), PyBroP™ (0.400g) were stirred under nitrogen in dimethylformamide (15ml). N,N-Diisopropylethylamine (0.171g) was added and left to stir for 2 hours. 1M sodium hydroxide was added to the reaction, with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to leave product plus dimethylformamide. Water was added which resulted in precipitation of the product. The product was filtered and was purified by RPHPLC (75%-5%, 0.1% ammonium acetate/ acetonitrile). After removal of the solvent under reduced pressure the resulting white solid was triturated with diethyl ether, filtered and dried to leave *N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]acetamide (0.067g; m.p. 145°C).

Example 360

N-[1-(4-Bromobenzyl)-4-piperidinyl]-2-(4-fluorophenyl)acetamide

2-(4-Fluorophenyl)-*N*-(4-piperidinyl)acetamide (WO97/36871; 1.00g), 1-bromo-4-(bromomethyl)benzene (1.06g) and potassium carbonate (0.877g) in dimethylformamide (15ml) were heated to 70°C, under nitrogen for 1 hour. Water was added to the reaction, with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to leave a cream solid. This solid was triturated with diethyl ether, filtered and recrystallised from ethanol/ water to give white crystalline needles of *N*-[1-(4-bromobenzyl)-4-piperidinyl]-2-(4-fluorophenyl)acetamide (m.p. 144°C).

Example 361

2-(4-Fluorophenyl)-*N*-[1-(2-quinolinylmethyl)-4-piperidinyl]acetamide

2-(4-Fluorophenyl)-*N*-(4-piperidinyl)acetamide (WO97/36871; 0.05g), 2-quinolinecarbaldehyde (0.033g) and sodium triacetoxyborohydride (0.067g) in dichloroethane (3ml) were stirred under nitrogen for 24 hours. Saturated sodium hydrogen carbonate was added to the reaction, with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure, triturated with diethyl ether/ ethyl acetate and filtered to leave 2-(4-fluorophenyl)-*N*-[1-(2-quinolinylmethyl)-4-piperidinyl]acetamide (0.020g).

Example 362

N-[1-(3-Chloro-4-fluorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide

3-[3-(2-Pyridinyl)-1,2,4-oxadiazol-5-yl]propanoic acid (0.218g) and N,N'-carbonyldiimidazole (0.194g) were stirred in dichloromethane (10ml) under nitrogen for 1 hour. 1-(3-Chloro-4-fluorobenzyl)-4-piperidinamine (JP 59101483; 0.242g) was then added and left to stir for 24 hours. Saturated sodium hydrogen carbonate was added to the reaction, with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure, triturated with ethyl acetate/ ethanol and filtered to leave *N*-[1-(3-chloro-4-fluorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide (m.p. 150°C).

Example 363

N-[1-(4-Chloro-3-fluorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide

Step i: *tert*-Butyl 1-(4-chloro-3-fluorobenzyl)-4-piperidinylcarbamate

4-Chloro-3-fluorobenzaldehyde (0.793g) and *tert*-butyl 4-piperidinylcarbamate (1.00g) were stirred under nitrogen in dried tetrahydrofuran (25ml). Sodium triacetoxyborohydride (1.266g) was then added and left for 24 hours. Saturated sodium hydrogen carbonate was added to the reaction, with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to leave *tert*-butyl 1-(4-chloro-3-fluorobenzyl)-4-piperidinylcarbamate (1.80g) as a white solid.

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Step ii: 1-(4-Chloro-3-fluorobenzyl)-4-piperidinamine

tert-Butyl 1-(4-chloro-3-fluorobenzyl)-4-piperidinylcarbamate (1.80g) in dichloromethane (20ml) was stirred under nitrogen. Trifluoroacetic acid (5ml) was then added dropwise and the reaction was left to stir for 2 hours. 1M sodium hydroxide was added to the reaction until basic, with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. Product purified by chromatography (5% ethanol/ dichloromethane to 10% ethanol/ dichloromethane) and solvent removed under reduced pressure to leave an oil which crystallised over the period of 48 hours. The resulting solid was triturated with diethyl ether and filtered to leave 1-(4-chloro-3-fluorobenzyl)-4-piperidinamine (0.500g) as a white solid.

Step iii: N-[1-(4-Chloro-3-fluorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide

3-[3-(2-Pyridinyl)-1,2,4-oxadiazol-5-yl]propanoic acid (0.136g) and N,N'-carbonyldiimidazole (0.114g) were stirred in dichloromethane (10ml) under nitrogen for 1 hour. 1-(4-Chloro-3-fluorobenzyl)-4-piperidinamine (0.150g) was then added and left to stir for 2 hours. Saturated sodium hydrogen carbonate was added to the reaction, with the resulting solution being extracted three times with dichloromethane. The pooled organic phases were washed once with water, once with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to leave an oil. This was triturated with diethyl ether which caused product the to crystallise. After filtration, the product was washed with diethyl ether and dried to N-[1-(4-chloro-3-fluorobenzyl)-4-piperidinyl]-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide (m.p. 132°C).

Example 364

2-(4-Chlorophenoxy)-N-[1-[(3,4-dichlorophenyl)methyl]-piperidin-4-yl]-acetamide

The product from Example A step (ii) was dissolved in dichloromethane (10ml) containing triethylamine (0.081g) and the solution was cooled to 0°C. 4-Chlorophenoxyacetyl chloride (88mg) in dichloromethane (3ml) was added dropwise, the cooling bath was removed and the resulting solution was stirred for 1hour. Ethyl acetate, water and brine were added and the phases were separated. The organic phase was dried, filtered and evaporated to give an oil which was purified by reverse phase HPLC (with a

gradient eluent system (25% MeCN/NH_4OAc_{aq} (0.1%) to 95% MeCN/NH_4OAc_{aq} (0.1%)) to give the title compound (0.049g).

Example 365

N-(1-benzyl-4-piperidinyl)-3-[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]propanamide

To a solution of 3-(3-pyridin-2-yl-[1,2,4]oxadiazol-5-yl)-propionic acid (1g) in tetrahydrofuran (5ml), was added carbonyldiimidazole (0.74g). The mixture was stirred for 10 minutes before addition of 1-benzyl-piperidin-4-ylamine (1ml) in tetrahydrofuran (5ml). The reaction mixture was stirred for 15 minutes then partitioned between ethyl acetate (20ml) and water (20ml). The organic layer was separated, dried ($MgSO_4$) and solvent removed by evaporation. Purification by Biotage® 40S eluting 3%MeOH/0.5% 880 ammonia/dichloromethane gave the title compound (0.93g).

Example 366

N-(2-{[1-(3,4-Dichloro-benzyl)-piperidin-4-yl]-methyl-amino}-ethyl)-2-(2-fluoro-phenyl)-acetamide

Step i: (2-Methylamino-ethyl)-carbamic acid tert -butyl ester

To a solution of (2-amino-ethyl)-carbamic acid-*tert*-butyl ester (5g) and triethylamine (6.5ml) in tetrahydrofuran (1000ml) at 0^0C was added methyliodide (1.94ml) dropwise over a period of 1 hour. The mixture was allowed to warm to ambient temperature and stirred for 72 hours before removal of solvents by evaporation. The residue was partitioned between ethyl acetate and water. The organic layer was separated, dried ($MgSO_4$) and solvent removed by evaporation to give the title compound (3.7g).

Step ii: (2-{[1-(3,4-Dichloro-benzyl)-piperidin-4-yl]-methyl-amino}-ethyl)-carbamic acid *tert*-butyl ester

To a solution of dichlorobenzyl- piperidin-4-one (Example 74, step (i), 4.8g) and acetic acid (1ml) in dichloromethane (100ml) was added (2-methylamino-ethyl)-carbamic acid *tert*-butyl ester (3.26g) and the mixture was stirred for 5 minutes before addition of sodium triacetoxyborohydride (7.9g). The reaction mixture was stirred for 12 hours before addition of sodium bicarbonate solution. The mixture was stirred for ½ hour and then partitioned between water and dichloromethane. The organic layer was separated, dried ($MgSO_4$) and solvent removed by evaporation. Purification by Biotage® 40S eluting 10%MeOH/2% triethylamine/dichloromethane gave the title compound (1.7g).

Step iii: N^1-[1-(3,4-Dichloro-benzyl)-piperidin-4-yl]-N^1-methyl-ethane-1,2-diamine

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(2-{[1-(3,4-Dichloro-benzyl)-piperidin-4-yl]-methyl-amino}-ethyl)-carbamic acid *tert*-butyl ester (1.7g) was dissolved in 6M HCl (20ml) and stirred for 12 hours. The solvent was evaporated and the residue was azeotroped with toluene and then sodium bicarbonate solution was added. The mixture was stirred for 10 minutes and the product was extracted with dichloromethane. The solvent was removed by evaporation to give the title compound (0.75g).

Step iv: *N*-(2-{[1-(3,4-Dichloro-benzyl)-piperidin-4-yl]-methyl-amino}-ethyl)-2-(2-fluoro-phenyl)-acetamide

Prepared by the method of Example 359 step (ii) using N^1-[1-(3,4-Dichloro-benzyl)-piperidin-4-yl]-N^1-methyl-ethane-1,2-diamine and 2-fluorophenylacetic acid.

Example 367

N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-*N*-methyl-2-(4-fluorophenyl)acetamide

Step i: [1-(3,4-Dichlorobenzyl)-piperidin-4-yl]-methyl-amine

To a solution of 1-(3,4-Dichloro-benzyl)-piperidin-4-one (3.1g) in dichloromethane (50ml) and acetic acid (0.69ml) was added methylamine (6ml of a 1M solution in tetrahydrofuran). The mixture was stirred for 5 minutes before the addition of sodium triacetoxyborohydride (3g) and the resulting mixture stirred for 72 hours. Sodium bicarbonate solution (100ml) added and the mixture stirred vigorously for 5 minutes before extraction of the product with dichloromethane (2X200ml). The organics were separated, bulked and dried, ($MgSO_4$). Purification by Biotage® 40S eluting 10%MeOH/0.5% 880 ammonia/dichloromethane gave the sub-title compound (1.8g).

Step ii: *N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-(4-fluorophenyl)acetamide

To a solution of 4-fluorophenylacetic acid (100mg) in tetrahydrofuran (3ml) was added carbonyldiimidazole (105mg). The mixture was stirred for 10 minutes before addition of [1-(3,4-dichlorobenzyl)-piperidin-4-yl]-methyl-amine (177mg) in tetrahydrofuran (2ml). Stirring was continued for 1 hour then solvent removed by evaporation. Purification by Biotage® 40S eluting 2%MeOH/0.5% 880 ammonia/dichloromethane gave the title compound (166mg).

Example 368

N-[1-[(3,4-dichlorophenyl)methyl]-4-piperidinyl]-2-(2-pyrimidinyloxy)-acetamide

Step i: Ethyl 2-pyrimidinyloxyacetate

Ethyl glycolate (1.04g) was dissolved in tetrahydrofuran (10ml) and the solution was cooled to 0°C. Sodium hydride (60% suspension in oil, 0.43g) was added and the suspension was stirred and then sonicated in an ultrasonic bath. 2-Chloropyrimidine (1.14g) was added and the mixture was sonicated for a further 110min. Ammonium chloride solution was added and the mixture was extracted thrice with ethyl acetate, the organic phases were washed with brine and dried, filtered and evaporated. The residue was purified by chromatography eluting with *iso*-hexane: ethyl acetate (13:7) to give the subtitle compound (1.40g) as an oil.

Step ii: 2-Pyrimidinyloxyacetic acid

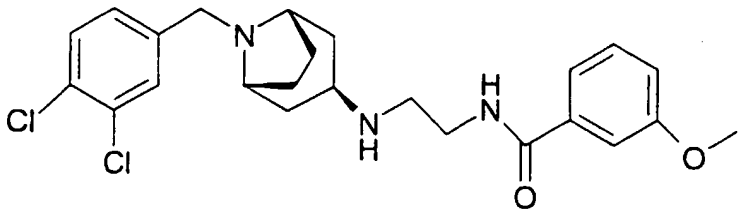
Ethyl 2-pyrimidinyloxyacetate (1.4g) was dissolved in ethanol (10ml). Sodium hydroxide (2M aq) was added and the mixture was stirred for 64h. The solvent was evaporated and the reside was dissolved in water, filtered and the acidified with concentrated hydrochloric acid. The resulting precipitate was collected and dried to give the subtitle compound (0.698g).

Step iii: *N*-[1-[(3,4-dichlorophenyl)methyl]-4-piperidinyl]-2-(2-pyrimidinyloxy)-acetamide

The title compound was prepared from the product of Example A step (ii) (hydrochloride salt, 335mg) and 2-pyrimidinyloxyacetic acid (170mg) using the method of Example 94. Yield 140mg, m.p. 120-122°C.

Example 369

N-[2-[[8-[(3,4-Dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]amino]ethyl]-3-methoxy-benzamide, bis toluene sulfonic acid salt



Step i: 8-[(3,4-Dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-one

2,5-Dimethoxytetrahydrofuran (4.92g) was stirred in hydrochloric acid (1M, 25 ml) for 1hour. 3,4-Dichlorobenzylamine (5ml) was added to hydrochloric acid (1M, 15ml) and the resulting suspension was added to the first solution. Phosphate buffer solution (pH 5.5, 250ml) was added followed by sodium hydroxide (1.6g). A solution of acetone

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dicarboxylic acid (4.77g) in phosphate buffer solution (pH 5.5, 90ml) was added to the mixture and the solution was stirred. A yellow solid formed and the mixture was left to stand for 64h. The aqueous supernatant was decanted and hydrochloric acid (2.5M) was added to the solid along with ethyl acetate. The layers were separated and the aqueous phase was extracted twice with dichloromethane containing a little methanol. The organic layers were combined and evaporated to give a crude oil (ca 7g). A portion of the product (ca 2.5g) was purified by chromatography eluting with dichloromethane : methanol (19:1) to give the subtitle compound (1.62g) as a yellow oil.

Step ii: Carbamic acid, Endo-[2-[[8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]amino]ethyl]-1,1-dimethylethyl ester

8-[(3,4-Dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-one (751 mg) and carbamic acid, (2-aminoethyl)-1,1-dimethylethyl ester (520 mg) were dissolved in dichloroethane (23ml). Sodium triacetoxyborohydride (697 mg) was added and the suspension was stirred at room temperature for 20hours. Dichloromethane was added and the solution was washed with sodium bicarbonate solution, then with water and then with brine. Chromatography of the residue eluting with ethyl acetate : methanol : triethylamine (80:19:1) gave the subtitle compound (688mg) as an oil.

Step iii: *N*-[2-[[8-[(3,4-Dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]amino]ethyl]-3-methoxy-benzamide, bis toluene sulfonic acid salt

Carbamic acid, [2-[[8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]amino]ethyl]-, 1,1-dimethylethyl ester (337mg) was dissolved in dichloromethane (3ml) and trifluoroacetic acid (3ml) was added. The resulting solution was stirred for 1hour then the volatiles were evaporated. The residue was dissolved in dichloromethane (3ml) and triethylamine (1ml) was added followed by 3-methoxybenzoyl chloride (120µl). The solution was stirred overnight. The solvent was evaporated and the residue was purified by RPHPLC (gradient ammonium acetate 1% aqueous : acetonitrile (25% acetonitrile to 95% acetonitrile)). Excess tosic acid in ether was added to the residue and the resultant salt was recrystallised from a mixture of ethyl acetate – ethanol with a little cyclohexane to give the title compound (77mg; m.p. 180-182.5°C).

Example 370

Endo-*N*-[8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]-3-(2-pyridinyl)-1,2,4-oxadiazole-5-propanamide hydrochloride

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Step i: Endo-8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-amine

8-[(3,4-Dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-one (350mg) was dissolved in dry methanol (12ml) and ammonium acetate (1g) was added. The mixture was stirred to get partial solution and then sodium cyanoborohydride (106mg) was added. The mixture was heated under reflux for 150 minutes, then allowed to cool to room temperature. The methanol was evaporated, the residue was partitioned between sodium hydroxide and dichloromethane, and the aqueous phase was extracted twice with dichloromethane. The organic phases were combined, dried, filtered and evaporated to give the subtitle compound.

Step ii: Endo-*N*-[8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]-3-(2-pyridinyl)-1,2,4-oxadiazole-5-propanamide hydrochloride

3-(2-Pyridinyl)-1,2,4-oxadiazole-5-propanoic acid (305mg) was suspended in dichloromethane (6ml) and oxalyl chloride (0.5ml) was added. The mixture was stirred overnight. Toluene (1ml) was added to the solution, the volatiles were evaporated, then the residue was redissolved in dichloromethane (2ml). Endo-8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-amine (all from step(i)) was dissolved in dichloromethane (4ml) containing triethylamine (0.5ml) and then cooled in an ice bath. The acid chloride solution was added to the amine and the mixture was stirred for 1hour. Water was added to the reaction mixture and the phases were separated. The aqueous phase was extracted twice with dichloromethane, the organic phases were dried, filtered and evaporated. The residue was purified by RPHPLC (gradient ammonium acetate 1% aqueous : acetonitrile (25% acetonitrile to 95% acetonitrile)). The product was suspended in ether and the ethereal hydrochloric acid was added, the suspension was stirred and then the diethyl ether was evaporated. The residue was dissolved in hot ethyl acetate containing ethanol and crystallisation was induced by adding *iso*-hexane to give the title compound (47mg).

Example 371

2-[4-(acetylamino)phenoxy]-*N*-[1-[(3,4-dichlorophenyl)methyl]-4-piperidinyl]-acetamide

Step i: Methyl (4-acetaminophenoxy)acetate

4-Acetaminophenol (1.51g), potassium carbonate (1.38g) and methyl bromoacetate (1.0ml) were combined in acetone (40ml) and heated to reflux for 5hours. The mixture was allowed to cool to room temperature, filtered and evaporated. The residue was

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dissolved in ethyl acetate, washed with water and then with brine then dried, filtered and evaporated to give the subtitle compound (2.32g).

Step ii: (4-Acetaminophenoxy)acetic acid

Methyl (4-acetaminophenoxy)acetate was hydrolysed following the method of Example 368 step (ii) to give the subtitle compound (1.85g).

Step iii: 2-[4-(acetylamino)phenoxy]-*N*-[1-[(3,4-dichlorophenyl)methyl]-4-piperidinyl]-acetamide

The title compound was prepared from the product of Example A step (ii) (free base, 281mg) and (4-acetaminophenoxy)acetic acid (229mg) using a method hereinbefore described (yield 40mg; m.p. 177-178.5°C).

Example 372

N-[1-[(3,4-dichlorophenyl)methyl]-4-piperidinyl]-4-hydroxy- benzeneacetamide

The title compound was prepared from the product of Example A step (ii) (free base, 172mg) and 4-hydroxyphenylacetic acid (135mg) using a method hereinbefore described (yield 57mg; m.p. 72-97°C).

Example 373

Exo-*N*-[8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]-3-(2-pyridinyl)-1,2,4-oxadiazole-5-propanamide

Step i: Endo-8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-ol

8-[(3,4-Dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-one (330mg) was dissolved in tetrahydrofuran (5ml) and cooled to 0°C. Lithium tris (3-ethylpentyl-3-oxy)aluminohydride solution (0.5M, 2.5ml) was added dropwise and the mixture was allowed to attain room temperature overnight. Sodium sulfate decahydrate (ca 2g) was added and the suspension was stirred for 1hour. The reaction mixture was diluted with ethyl acetate, filtered through kieselguhr and evaporated. The residue was purified by chromatography eluting with dichloromethane: methanol (9:1) to give the subtitle compound 161mg.

Step ii: Exo-2-[8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]-1*H*-isoindole-1,3(2*H*)-dione

Endo-8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-ol (556mg), phthalimide (321mg) and polymer bound triphenylphosphine (821mg) were combined in tetrahydrofuran (10ml). Diethylazodicaboxylate (330µl) was added and the mixture was

stirred gently overnight. Additional phosphine (0.5g) and diethylazodicaboxylate (200µl) were added and the mixture was stirred for an additional 5 days. The reaction mixture was diluted with ethyl acetate and filtered; the residue was washed with ethyl acetate and methanol. The filtrate was evaporated, and chromatographed eluting with 9:1 ethyl acetate : methanol. RPHPLC of the product (gradient ammonium acetate 1% aqueous : acetonitrile (25% acetonitrile to 100% acetonitrile)) gave the subtitle compound (90mg).

Step iii: Exo-8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-amine

Exo-2-[8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]-1*H*-isoindole-1,3(2*H*)-dione (90mg) was dissolved in ethanol (6ml) containing dichloromethane (3ml); hydrazine hydrate (0.2ml) was added and the resulting solution was stirred at room temperature for 26hours. The suspension was filtered and the filtrate was evaporated to give the subtitle compound (55mg).

Step iv: Exo-*N*-[8-[(3,4-dichlorophenyl)methyl]-8-azabicyclo[3.2.1]oct-3-yl]-3-(2-pyridinyl)-1,2,4-oxadiazole-5-propanamide

Prepared following the method of Example 370 step (iii) but without salt formation to give the title compound (15mg; m.p. 177.5-178°C).

Example 374

(R) *N*-[1-[1-(4-bromophenyl)ethyl]-4-piperidinyl]-3-(2-pyridinyl)-1,2,4-oxadiazole-5-propanamide

Step i: (R)-1-[1-(4-Bromophenyl)ethyl]-4-piperidinone

(R)-(4-Bromophenyl)ethylamine (1.01g) and potassium carbonate (1.45g) were dissolved in a mixture of ethanol (13ml) and water (6ml) and then heated to a vigorous reflux. A solution of 4-hydroxy-4-methoxy-1,1-dimethyl-piperidinium iodide (J. Chem. Soc. Perkin Trans. 2, (1984) 1647) (1.47g) in warm water (6ml) was added dropwise over 40 minutes; reflux was maintained for a further 12hours, then the reaction was allowed to cool to room temperature. The mixture was evaporated and ethyl acetate and water were added and the phases were separated. The aqueous phase was extracted twice with ethyl acetate, the organic layer was washed with brine, dried, filtered and evaporated. Chromatography of the residue eluting with *iso*-hexane : ethyl acetate (3:2) gave the subtitle compound (804mg).

Step ii: (R)-1-[1-(4-Bromophenyl)ethyl]-4-piperidinamine

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Prepared following the general method of Example 370 step (i) (R)-1-[1-(4-bromophenyl)ethyl]-4-piperidinone (420mg) ammonium acetate (0.80g) and sodium cyanoborohydride (120mg) to give the subtitle compound (449mg).

Step iii: (R) *N*-[1-[1-(4-bromophenyl)ethyl]-4-piperidinyl]-3-(2-pyridinyl)-1,2,4-oxadiazole-5-propanamide

Prepared following a method as hereinbefore described using (R)-1-[1-(4-bromophenyl)ethyl]-4-piperidinamine (449mg), 3-(2-pyridinyl)-1,2,4-oxadiazole-5-propanoic acid (0.31g), 1-hydroxybenzotriazole (0.20g), 4-(N,N-dimethylamino)-pyridine (0.13g) and 1-ethyl-3-[3-(dimethylamino)-propyl]carbodiimide hydrochloride (0.30g) to give the title compound (40mg; m.p. 153-155°C).

Example 375

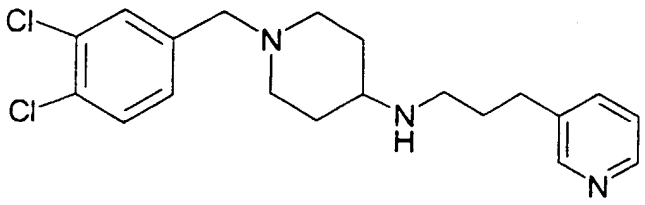
(S) *N*-[1-[1-(4-bromophenyl)ethyl]-4-piperidinyl]-3-(2-pyridinyl)-1,2,4-oxadiazole-5-propanamide

Prepared following an analogous series of steps to example 374 but using (S)-(4-bromophenyl)ethylamine to give the title compound. m.p. 141.5-143°C

α_D −29.55° (c= 0.13, methanol, 21°C)

Example 385

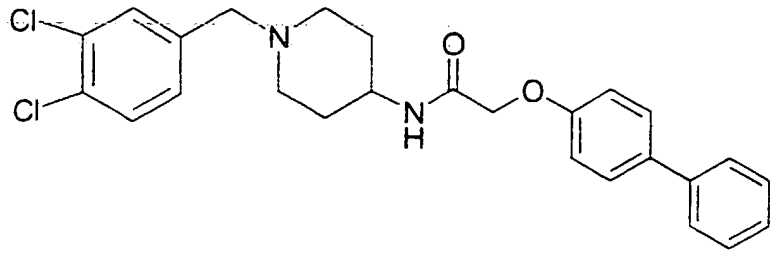
1-[3,4-Dichlorobenzyl]-N-[3-(3-pyridinyl)propyl]-4-piperidinamine



The title compound was prepared from 1-(3,4-dichlorobenzyl)piperidine-4-amine (free base 187mg) , 3-(3-pyridinyl)propanal (125mg), sodium triacetoxyborohydride (70mg), and 0.02ml acetic acid, stirred together for 2hrs in dichloromethane (10ml). Water was added, the mixture neutralised with sodium bicarbonate and the organic phase separated, dried and chromatographed on silica with ethyl acetate/methanol (9:1) as eluant, to give the title compound (70mg) as a colourless oil.

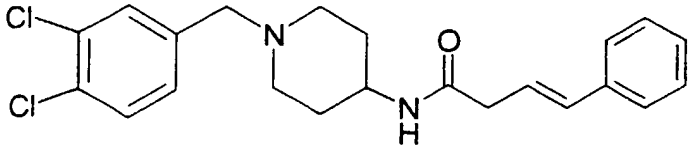
Example 386

2-[(1,1'-Biphenyl)-4-yloxy]-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]acetamide



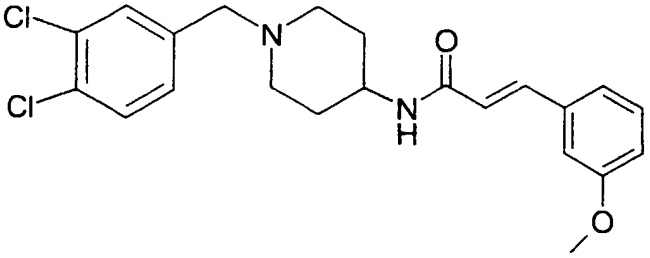
Example 387

N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-4-phenyl-3-butenamide



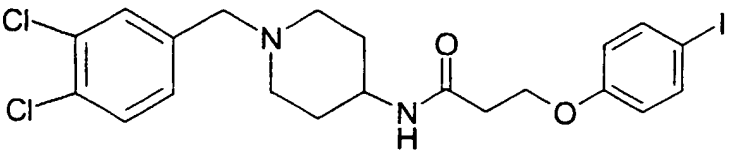
Example 388

N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-3-(3-methoxyphenyl)-2-propenamide.



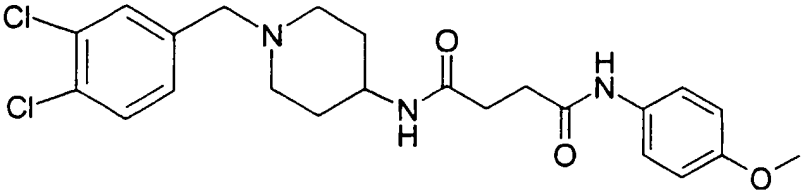
Example 389

N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-3-(4-iodophenoxy)propanamide.



Example 390

N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-N'-(4-methoxyphenyl)succinamide



Example 391

N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-[(5-phenyl-2-pyrimidinyl)oxy] acetamide

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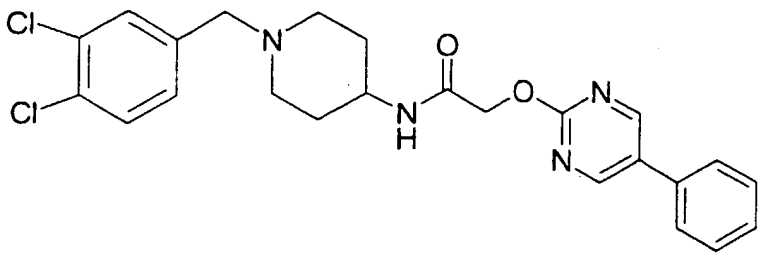
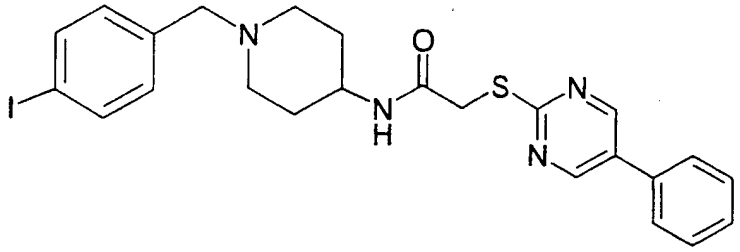


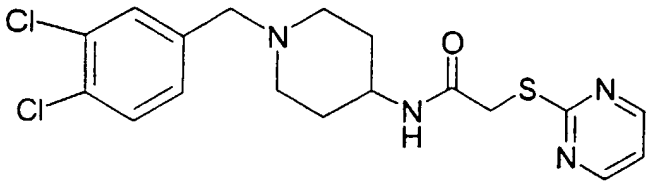
Example 392

N-[1-(4-iodobenzyl)-4-piperidinyl]-2-(5-phenyl-2-pyrimidinyl)thio]acetamide



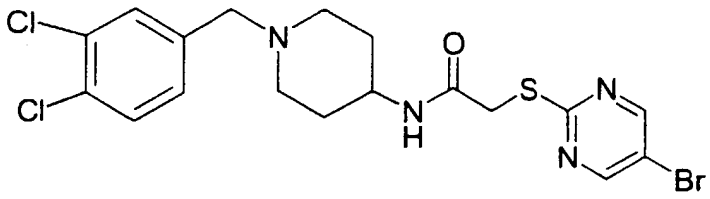
Example 393

N-[1-(3,4-dichlorobenzy)-4-piperidinyl]-2-[(2-pyrimidinyl)thio]acetamide



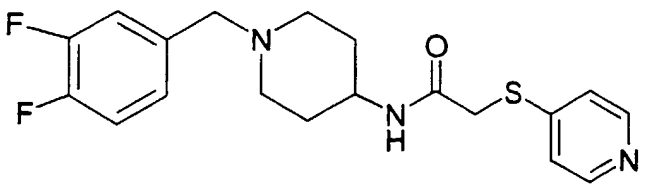
Example 394

2-[(5-Bromo-2-pyrimidinyl)thio]-N-[1-(3,4-dichlorobenzy)-4-piperidinyl]acetamide



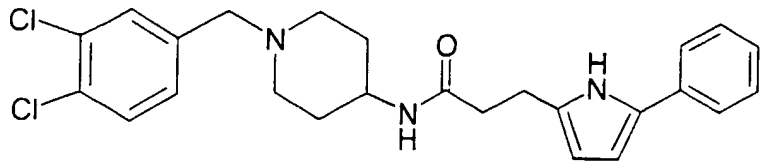
Example 395

N-[1-(3,4-difluororobenzyl)-4-piperidinyl]-2-(4-pyridinylthio)acetamide



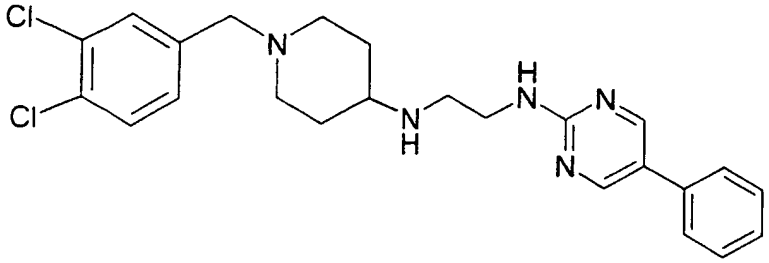
Example 396

N-[1-(3,4-dichlorobenzy)-4-piperidinyl]-3-(5-phenyl-1H-pyrrol-2-yl)propanamide



Example 397

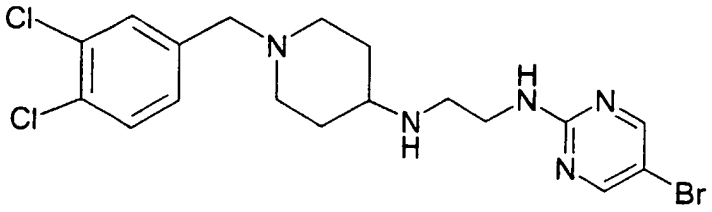
N-[1-(3,4-dichlorobenzy)-4-piperidinyl]-N'-(5-phenyl-2-pyrimidinyl)-1,2-ethandiamine



The title compound (20mg) was prepared by heating at reflux N^1-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-1,2-ethanediamine (100mg) and 2-chloro-5-phenypyrimidine (100mg) and Hunigs' base (100mg) in toluene for 8hours. The mixture was purified by chromatography on silica, with ethyl acetate methanol (9:1) as eluant to give the title compound as a yellow oil.

Example 398

N-[5-bromo-2-pyrimidinyl]-N'-[1-(3,4-dichlorobenzy)-4-piperidinyl]- 1,2-ethandiamine



Prepared by the method of Example 397 amine (200mg), 2-chloro-5-bromopyrimidine (130mg), Hunigs' base (200mg) to give the title compound (20mg).

Example 399

2-[(2-Chloro-4-pyrimidinyl)amino]-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl] acetamide

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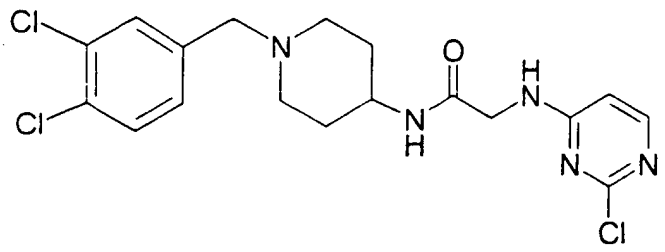
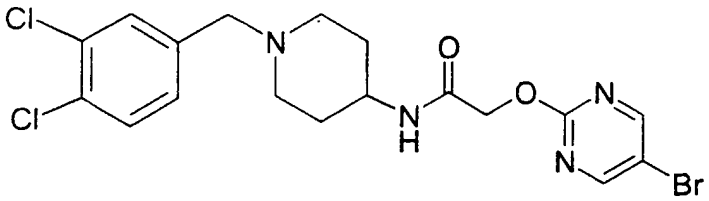


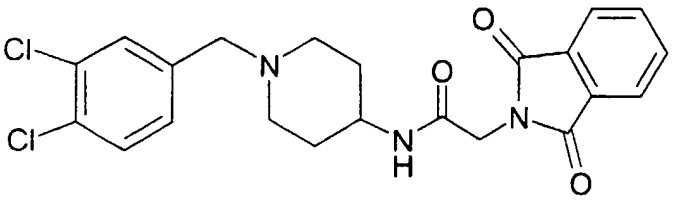
Example 401

2-[(5 -Bromo-2-pyrimidinyl)oxy]-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-acetamide.



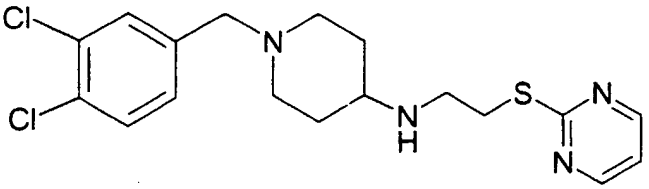
Example 402

N-[1-(3,4-dichlorobenzy)-4-piperidinyl]-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)acetamide



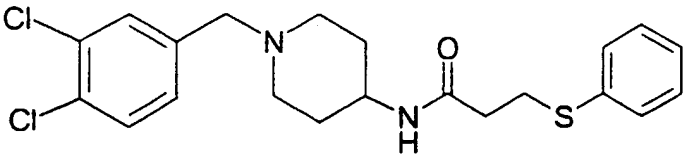
Example 403

N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-N-[2-(2-pyridinylthio)ethylamine, dihydrochloride



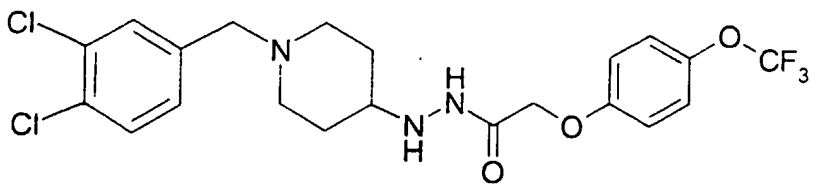
Example 404

N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-3-(phenylthio)propanamide



Example 405

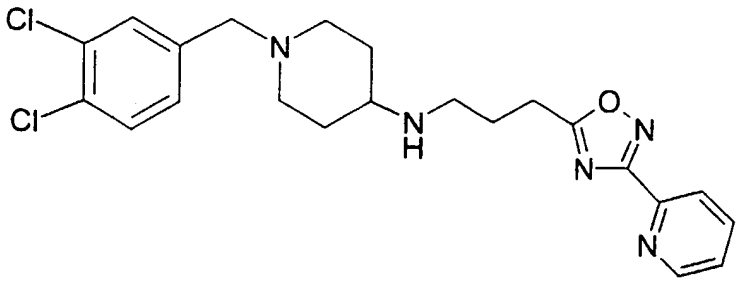
N'-[1-(3,4-dichlorobenzyl)- 4-piperidinyl]-2-[4-(trifluoromethoxy)phenoxy] acetohydrazide



The title compound was prepared from 3,4-dichlorobenzyl-4-piperidone (J. Med. Chem, 1999, **42**, 3629; 100mg), 2-[4(trifluoromethoxy)phenoxy]acetohydrazide (100mg), sodium triacetoxyborohydride (100mg), and 0.02ml acetic acid, stirred together for 2hours in dichloromethane by the method of Example 369 step ii.

Example 406

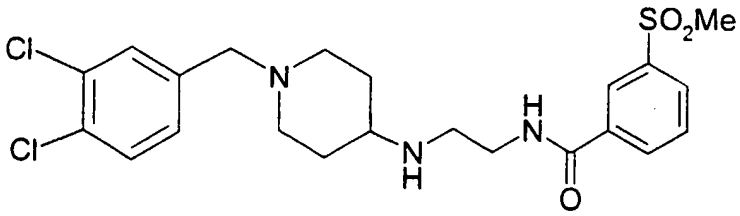
N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-N-[3-[3-(2-pyridinyl)-1,2,4-oxadiazo-5-yl]propyl]amine



The title compound (29mg) was prepared from 3,4-dichlorobenzylpiperidine-4-amine (100mg free base), 2-[5-(3-bromopropyl)-1,2,4-oxadiazol-3-yl]pyridine (100mg), potassium carbonate (100mg) in dimethyl formamide (1ml) were heated together in the microwave for 30secs,water was added and the product extracted into dichloromethane and chromatographed on silica with ethyl acetate/methanol(9:1) as eluant.

Example 407

N-[2-[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino]ethyl]-3-(methylsulphonyl)benzamide



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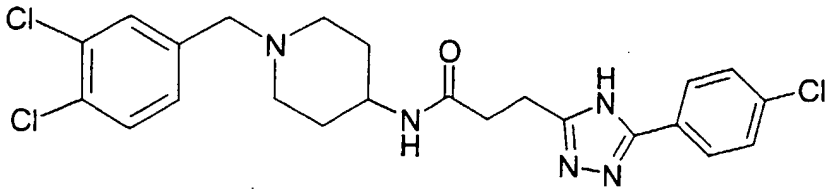
Prepared from *N*-(2-aminoethyl)-*N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2,2,2-trifluoroacetamide (100mg), 3-methylsulphonylbenzoic acid (50mg) and carbonyldiimidazole (40mg). The product obtained was stirred together with sodium hydroxide (40mg) in 50:50 methanol/ water for 12hrs, extracted into dichloromethane and purified by chromatography on silica with ethyl acetate/methanol (9:1) as eluant, to give the title compound (25mg).

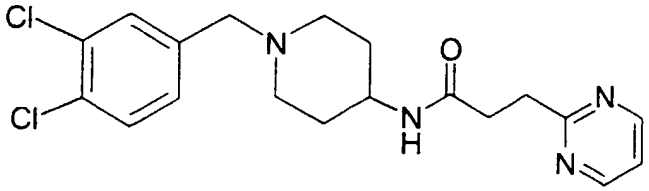
Example 408

3-[5-(4-chlorophenyl)-4H-1,2,4-triazol-3-yl]-N-[1-(3,4-dichlorobenzyl)-4-piperidinyl] propanamide



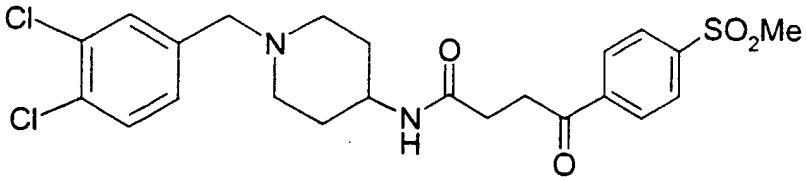
Example 409

N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-3-(2-pyridinyl)propanamide



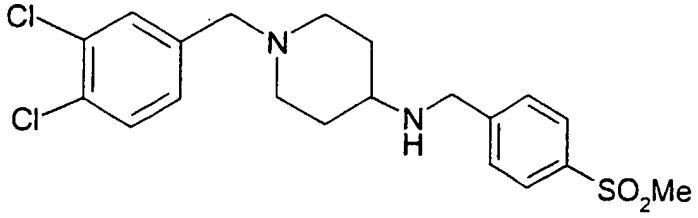
Example 410

N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-4-(4-(methylsulphonyl)phenyl-4-oxobutanamide



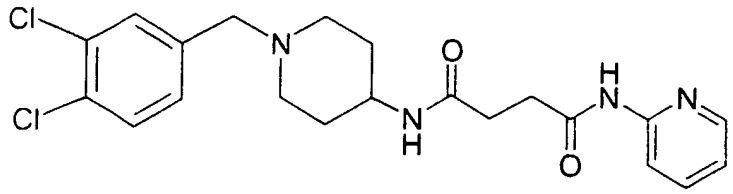
Example 411

N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-N'-[4-(methylsulphonyl) benzylamine



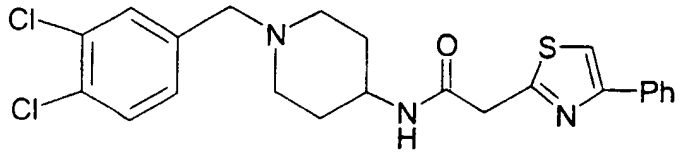
Example 412

N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-N'-[(2-pyridinyl) succinamide



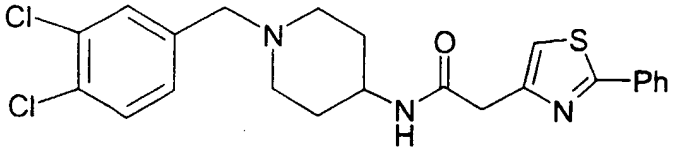
Example 413

N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-(4-phenyl-1,3-thiazol-2-yl))acetamide



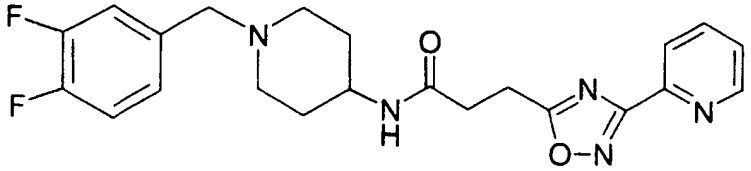
Example 414

N-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2-(2-phenyl-1,3-thiazol-4-yl))acetamide



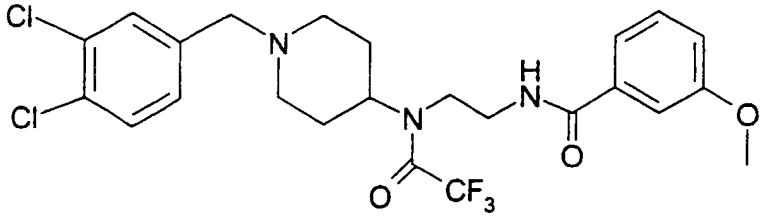
Example 415

N-[1-(3,4-difluorobenzyl)-4-piperidinyl]-3-(3-2-pyridinyl-1,2,4-oxadiazol-5-yl]propanamide



Example 416

N-trifluoroacetyl–N-[2-[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino]ethyl]-3-methoxybenzamide



a) tert-butyl 2-{[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino}ethylcarbamate

The sub-title compound (800mg) was prepared from 3.4-dichlorobenzyl-4-piperidone (1.3g) *tert*-butyl 2-aminoethylcarbamate (0.8g), sodium triacetoxyborohydride (100mg), and 0.02ml acetic acid, stirred together for 2hrs in dichloromethane. The sub-titled compound was isolated by standard procedures.

MS $[M+H]^+$ (ES+) 402

b) N-(2-aminoethyl)-*N*-[1-(3,4-dichlorobenzyl)-4-piperidinyl]-2,2,2-trifluoroacetamide

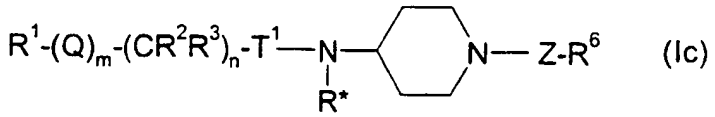
A mixture of the above amine (800mg), and triethylamine (0.5ml) in dichloromethane (50ml) , treated with trifluoroacetic anhydride (420mg) over 30 mins, evaporated to dryness and dichloromethane(20ml) and trifluoroacetic acid (2ml) added, stirred for 3hrs, then neutralised with aqueous sodium bicarbonate, the organic phase separated, dried and evaporated to give the title compound (250mg) as a yellow oil.

c) N-trifluoroacetyl–N-[2-[1-(3,4-dichlorobenzyl)-4-piperidinyl]amino]ethyl]-3-methoxybenzamide

The title compound (30mg) was prepared from the product above (40mg) 3-methoxybenzoyl chloride (20mg) and triethylamine (50mg) using one of the methods described above.

MS $[M+H]^+$ (ES+) 580

Further compounds of formula (I), all according to formula (Ic), are shown in the table below.



(Ic)

Example	R^1	$(Q)_m$	$(CR^2R^3)_n$	T^1	R*	Z	R^6
380	4-Cl-C_6H_4	O	CH_2	C(O)	H	CH_2C (O)NH	2-Cl-5-CH_3-C_6H_3
381	4-Cl-C_6H_4	O	CH_2	C(O)	H	$(CH_2)_3$	C_6H_5
382	3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl	O	CH_2	C(O)	H	allyl	C_6H_5
383	2-(cyclopropyl-NH)-pyrimidin-4-yl	m=0	n=0	-	CH_3	CH_2	3,4-Cl_2-C_6H_3

384	2-(pyridin-3-yl)-pyrimidin-4-yl	m=0	n=0	-	CH_3	CH_2	3,4-Cl_2-C_6H_3
400	pyrimidin-2-yl	S	CH_2	C(O)	H	C(O)	3,4-Cl_2-C_6H_3

EXAMPLE 417

A pharmaceutical combination comprising a compound of formula (I) (such as the compound of one of Examples 1 to 416; especially the compound of Example 99, 100, 102 or 415) and loratidine, desloratidine, fexofenadine, cetirizine, ebastine, astemizole, norastemizole, epinastine, efletirizine, budesonide, fluticasone, mometasone, rofleponide, montelukast, pranlukast, zafirlukast, Z4407, zafirlukast, recombinant human IL-10, recombinant human IL-12, formoterol, salmeterol, salbutamol, SB-207499, theophylline, an anti-IL-5 antibody or an anti-TNF-antibody.

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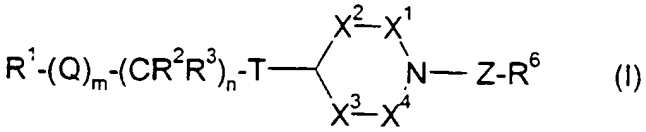
CLAIMS

1. A pharmaceutical combination comprising a compound of formula (I):



(I)

wherein

Z is CR^4R^5, C(O) or CR^4R^5-Z^1;

Z^1 is C_{1-4} alkylene (such as CH_2), C_{2-4} alkenylene (such as CH=CH) or C(O)NH;

R^1 represents a C_{1-12} alkyl group optionally substituted by one or more substituents independently selected from cyano, hydroxyl, C_{1-6} alkoxy (such as methoxy or ethoxy), C_{1-6} alkylthio (such as methylthio), C_{3-7} cycloalkyl (such as cyclopropyl), C_{1-6} alkoxycarbonyl (such as methoxycarbonyl) and phenyl (itself optionally substituted by one or more of halogen, nitro, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl (such as CF_3), phenyl(C_{1-6} alkyl) (such as benzyl), C_{1-6} alkoxy, C_{1-6} haloalkoxy, $S(O)_2(C_{1-6}$ alkyl), $C(O)NH_2$, carboxy or C_{1-6} alkoxycarbonyl); or

R^1 represents C_{2-6} alkenyl optionally substituted by phenyl (itself optionally substituted by one or more of halogen, nitro, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl(C_{1-6} alkyl), C_{1-6} alkoxy, C_{1-6} haloalkoxy, $S(O)_2(C_{1-6}$ alkyl), $C(O)NH_2$, carboxy or C_{1-6} alkoxycarbonyl); or

R^1 represents a 3- to 14-membered saturated or unsaturated ring system which optionally comprises up to two ring carbon atoms that form carbonyl groups and which optionally further comprises up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, wherein the ring system is optionally substituted by one or more substituents independently selected from: halogen, cyano, nitro, oxo, hydroxyl, C_{1-8} alkyl, C_{1-6} hydroxyalkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy(C_{1-6} alkyl), C_{3-7} cycloalkyl(C_{1-6} alkyl), C_{1-6} alkylthio(C_1-C_6 alkyl), C_{1-6} alkylcarbonyloxy(C_{1-6} alkyl), C_{1-6} alkyl$S(O)_2$(C_{1-6} alkyl), aryl(C_{1-6} alkyl), heterocyclyl(C_{1-6} alkyl), aryl$S(O)_2$(C_{1-6} alkyl), heterocyclyl$S(O)_2$(C_{1-6} alkyl), aryl(C_{1-6} alkyl)$S(O)_2$, heterocyclyl(C_{1-6} alkyl)$S(O)_2$, C_{2-6} alkenyl, C_{1-6} alkoxy, carboxy-substituted C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkoxy, C_{1-6} alkylcarboxy-substituted C_{1-6} alkoxy, aryloxy, heterocyclyloxy, C_{1-6} alkylthio, C_{3-7}

cycloalkyl(C_{1-6} alkylthio), C_{3-6} alkynylthio, C_{1-6} alkylcarbonylamino, C_{1-6} haloalkylcarbonylamino, SO_3H, NR^7R^8, $C(O)NR^{23}R^{24}$, $S(O)_2NR^{18}R^{19}$, $S(O)_2R^{20}$, $R^{25}C(O)$, carboxyl, C_{1-6} alkoxycarbonyl, aryl and heterocyclyl; wherein the foregoing aryl and heterocyclyl moieties are optionally substituted by one or more of halogen, oxo, hydroxy, nitro, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl(C_{1-6} alkyl), C_{1-6} alkoxy, C_1-C_6 haloalkoxy, $S(O)_2(C_{1-6}$ alkyl), $C(O)NH_2$, carboxy or C_{1-6} alkoxycarbonyl;

m is 0 or 1;

Q represents an oxygen or sulphur atom or a group NR^9, C(O), $C(O)NR^9$, $NR^9C(O)$ or CH=CH;

n is 0, 1, 2, 3, 4, 5 or 6 provided that when n is 0, then m is 0;

each R^2 and R^3 independently represents a hydrogen atom or a C_{1-4} alkyl group, or $(CR^2R^3)_n$ represents C_{3-7} cycloalkyl optionally substituted by C_{1-4} alkyl;

T represents a group NR^{10}, $C(O)NR^{10}$, $NR^{11}C(O)NR^{10}$ or $C(O)NR^{10}NR^{11}$;

X^1, X^2, X^3 and X^4 are, independently, CH_2, CHR^{12} {wherein each R^{12} is, independently, C_{1-4} alkyl or C_{3-7} cycloalkyl(C_{1-4} alkyl)} or C=O; or, when they are CHR^{12}, the R^{12} groups of X^1 and X^3 or X^4, or, X^2 and X^3 or X^4 join to form a two or three atom chain which is CH_2CH_2, $CH_2CH_2CH_2$, CH_2OCH_2 or CH_2SCH_2; provided always that at least two of X^1, X^2, X^3 and X^4 are CH_2;

R^4 and R^5 each independently represent a hydrogen atom or a C_1-C_4 alkyl group;

R^6 is aryl or heterocyclyl, both optionally substituted by one or more of: halogen, cyano, nitro, oxo, hydroxyl, C_{1-8} alkyl, C_{1-6} hydroxyalkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy(C_{1-6} alkyl), C_{3-7} cycloalkyl(C_{1-6} alkyl), C_1-C_6 alkylthio(C_{1-6} alkyl), C_{1-6} alkylcarbonyloxy(C_{1-6} alkyl), C_{1-6} alkyl$S(O)_2$(C_{1-6} alkyl), aryl(C_{1-6} alkyl), heterocyclyl(C_{1-6} alkyl), aryl$S(O)_2$(C_{1-6} alkyl), heterocyclyl$S(O)_2$(C_{1-6} alkyl), aryl(C_{1-6} alkyl)$S(O)_2$, heterocyclyl(C_{1-6} alkyl)$S(O)_2$, C_{2-6} alkenyl, C_{1-6} alkoxy, carboxy-substituted C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkoxy, C_1-C_6 alkylcarboxy-substituted C_{1-6} alkoxy, aryloxy, heterocyclyloxy, C_{1-6} alkylthio, C_{3-7} cycloalkyl(C_{1-6} alkylthio), C_{3-6} alkynylthio, C_{1-6} alkylcarbonylamino, C_{1-6} haloalkylcarbonylamino, SO_3H, $NR^{16}R^{17}$, $C(O)NR^{21}R^{22}$, $S(O)_2NR^{13}R^{14}$, $S(O)_2R^{15}$, $R^{26}C(O)$, carboxyl, C_{1-6} alkoxycarbonyl, aryl and heterocyclyl; wherein the foregoing aryl and heterocyclyl moieties are optionally substituted by one or more

of halogen, nitro, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl(C_{1-6} alkyl), C_{1-6} alkoxy, C_{1-6} haloalkoxy, $S(O)_2(C_{1-6}$ alkyl), $C(O)NH_2$, carboxy or C_{1-6} alkoxycarbonyl;

R^7, R^8, R^9, R^{10}, R^{11}, R^{13}, R^{14}, R^{16}, R^{17}, R^{18}, R^{19}, R^{21}, R^{22}, R^{23} and R^{24} are, independently hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-4} alkyl) or phenyl(C_{1-6} alkyl); and,

R^{15} and R^{20} are, independently, C_{1-6} alkyl, C_{1-6} hydroxyalkyl, C_{3-6} cycloalkyl, C_{3-7} cycloalkyl(C_{1-4} alkyl) or C_{1-6} alkyl optionally substituted by phenyl;

R^{25} and R^{26} are, independently, C_{1-6} alkyl or phenyl (optionally substituted by one or more of halogen, nitro, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl(C_{1-6} alkyl), C_{1-6} alkoxy, C_{1-6} haloalkoxy, $S(O)_2(C_{1-6}$ alkyl), $C(O)NH_2$, carboxy or C_{1-6} alkoxycarbonyl);

or a pharmaceutically acceptable salt thereof, or solvate thereof, or a solvate of a salt thereof;

provided that when T is $C(O)NR^{10}$ and R^1 is optionally substituted phenyl then n is not 0;

and a histamine antagonist, a steroid, a leukotriene modulator, a human cytokine, a beta-agonist, a phosphodiesterase inhibitor or an antibody.

2. A pharmaceutical combination as claimed in claim 1, wherein Q is a sulphur atom or a group NH, C(O) or NHC(O).

3. A pharmaceutical combination as claimed in claim 1 or 2, wherein T represents a group NH, C(O)NH or NHC(O)NH.

4. A pharmaceutical combination as claimed in claim 1, 2 or 3, wherein X^1, X^2, X^3 and X^4 are all CH_2.

5. A pharmaceutical combination as claimed in claim 1 wherein the compound of formula (I) is a compound of Example 1 to 416.

6. A pharmaceutical combination as claimed in any one of the preceding claims wherein:

the histamine antagonist is loratidine, desloratidine, fexofenadine, cetirizine, ebastine, astemizole, norastemizole, epinastine or efletirizine;
the steroid is budesonide, fluticasone, mometasone or rofleponide;
the leukotriene modulator is montelukast, pranlukast, zafirlukast, Z4407 or zafirlukast;
the human cytokine is recombinant human IL-10 or IL-12;
the beta-agonist is formoterol, salmeterol or salbutamol;
the phosphodiesterase inhibitor is SB-207499 or theophylline; or,
the antibody is an anti-IL-5 antibody or an anti-TNF-antibody.

7. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a histamine antagonist, a steroid, a leukotriene modulator, a human cytokine, a beta-agonist, a phosphodiesterase inhibitor or an antibody, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

8. A pharmaceutical combination as claimed in any one of claims 1 to 6 for use in therapy.

9. A pharmaceutical combination as claimed in any one of claims 1 to 6 in the manufacture of a medicament for the treatment of asthma or rhinitis.

Application No: GB 0104534.3 **Examiner:** Dr Annabel Ovens
Claims searched: 1-9 **Date of search:** 9 July 2002

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.T): A5B

Int Cl (Ed.7): A61K 31/4468, 31/4523, 31/4525, 31/453, 31/4535, 31/454, 31/4545, 31/46, 31/496, 31/497, 31/498, 31/506, 31/517, 31/519, 31/52

Other: Online: PAJ, EPODOC, WPI, CAS-ONLINE

Documents considered to be relevant:

Category	Identity of document and relevant passage		Relevant to claims
X, E	WO 02/32893 A2	(SCHERING) see page 10 lines 16-18, page 11 lines 3-20 and page 19 lines 6-16	1 at least
X, E	WO 01/60407 A2	(ASTA MEDICA) see page 7 lines 22-34	1 at least
X	WO 98/06394 A1	(SCHERING) see page 3 line 30-page 4 line 6, page 4 lines 17-29 and Examples 8-11	1 at least
X	US 6103735	(ASLANIAN AND PIWINSKI) see column 2 lines 45-54 and column 5 line 59-column 6 line 7	1 at least
X	CAPLUS Abstract Accession No. 2001:79915 & BioDrugs Vol. 14, No. 6, 2000, D Reichmuth and R Lockey, "Present and potential therapy for allergic rhinitis. A review", pages 371-387 (see abstract)		1 at least

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

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